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A NATIONAL HEALTH PROGRAM*

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WASHINGTON, DISTRICT OF COLUMBIA

YOU have come here, I believe, to find out what those who have been considering a national program of health have in mind, how it will work and what the results will be. I shall try to give you as much of this information as has been developed and can be supplied in a period of thirty minutes, and I shall make it as simple and direct as possible.

I assume that all of you know that proposals for a national health program have been made by an interdepartmental committee appointed by the President consisting of officials from the major federal departments most closely concerned with the provisions of the Social Security Act. A technical subcommittee on medical care was set up, and it was the report of the latter that formed the basis of the National Health Conference, which has stimulated nation-wide interest and discussion.

The purpose of the committee was to appraise the state of the nation's health and to arrive at conclusions as to what could and should be done to improve it. This was a logical course of action because in addition to the humanitarian elements involved, illness and death cost taxpayers money. The social security laws provide pensions for dependent children, some of whom may be made fatherless by the death of the bread-winner from tuberculosis or made motherless by death in childbirth. Pensions are paid for the blind. It is certainly not good business to pay pensions to persons made unemployable, dependent and destitute because of preventable illness without trying to do something to prevent the illness and restore the sick to health. This basic relation between health and economic welfare was recognized in the Social Security Act already in operation, and an annual appropriation of $12,000,000 for the United States Public Health Service and the Children's Bureau was authorized to aid the states in their efforts to improve the public health. A beginning has been made and commendable work is being done, but it will require a much greater effort to do what we know how to do along these lines.

We may take deep satisfaction in the brilliant advances that have been made in scientific knowledge and the practice of preventive and curative medicine. Our general death rate is the lowest on record. It has been reduced from 17.6 per thousand in 1900 to 11.5 in 1936, which represents a saving of about three quarters of a million lives in 1936 alone. During the same period, twelve years were added to the average expectation of life at birth. The saving, however, has been chiefly in the years of childhood and early adult life, when the preventable diseases are most frequent. Mortality in the higher ages has not in general been declining, and those who reach the age of fifty years or over have little reason to believe that they will live for more than a fraction of a year longer than if they had reached that age in 1900. In some of the important diseases of adult life the death rate has been increasing — in cancer, for example, and in diseases of the heart, blood vessels and kidneys.

Fine though the record has been, there are serious problems of health and medical care that yet remain to be solved, and new ones are constantly arising. It is with these and the possibilities of future accomplishments that we have to deal if unnecessary suffering and wastage of human life and resources are to be averted. Let us, then, review some of the findings that have been made, considering first those conditions within the field of public health for which known remedies are at hand.

EXPANSION OF PUBLIC-HEALTH AND MATERNAL AND CHILD-HEALTH SERVICES

Venereal Disease. The venereal diseases of course constitute our greatest health problem. Of syphilis especially much information has been received

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of late. I shall recall only a few of the more important facts.

A total of 518,000 persons newly infected with syphilis seek treatment each year. More than 1,000,000 seek treatment for gonorrhea. There are probably an equal number of sufferers from these diseases who do not seek treatment. Some 60,000 babies with syphilis are born each year. There are 40,000 deaths each year from syphilitic disease of the blood vessels and the heart, 80 per cent of which could be prevented by adequate treatment in the early stages. The cost of maintaining persons blinded by preventable syphilis is $10,000,000 a year. About 10 per cent of the patients in our hospitals for the insane are there because of syphilis. The annual cost of their care is about $31,500,000. Surgeon General Parran has stated that syphilis can be brought down to a small fraction of its present prevalence in a decade and essentially wiped out within a generation if the knowledge already available is effectively applied.

Pneumonia. Pneumonia stands third on the list of the causes of death. An average of 96,500 persons died from this disease each year from 1930 to 1935. The death rate is highest among infants and children of the pre-school ages, and among persons in late-middle and old age. Nearly 600,000 persons are disabled from it annually. Current experiments in the mass prevention of pneumonia by protective inoculation give great promise of success. In serum treatment and other methods the means are at hand to reduce greatly the mortality of and disability from the disease, even after it has been contracted. However, the laboratory facilities and the serum necessary for this expensive life-saving treatment are available in only a very few places to those who are unable to pay the cost.

Cancer. Cancer is second on the list of the causes of death, and claimed 143,000 victims in 1936. There are probably 400,000 persons in the United States today suffering from cancer. Under present conditions it is estimated that one of every eight persons who reaches the age of forty-five will die of cancer. Yet leading authorities have estimated that as many as 40,000 of these lives might be saved each year if all the patients received the benefits of modern methods of treatment, and if opportunity were provided for the diagnosis of a larger number of cases in the early stages.

Tuberculosis. There are still about 70,000 deaths from tuberculosis each year. Forty thousand of these occur among adults between the ages of forty and forty-five. Those qualified to judge are of the opinion that the deaths can be reduced by 50 per cent through the health supervision of workers in occupations predisposing to the disease, through the detection of incipient cases and through the provision of adequate medical and institutional care in the early stages. Most cases are discovered too late for effective treatment, and far too many reach sanatoriums when the disease has advanced too far for a hopeful outcome.

Diabetes. There are probably between 400,000 and 500,000 persons suffering from diabetes, with 30,000 deaths each year. If insulin can be made available to all those who need it, and properly administered with the other treatment indicated, deaths can be reduced and life prolonged.

Maternal and Infant Mortality. Today there is a great and unnecessary waste of maternal and infant life. Physicians after careful evaluation of the causes responsible for the deaths of mothers report that at least half the 14,000 deaths of women which occur each year from causes connected with pregnancy and childbirth can be prevented. About 75,000 infants are stillborn, and almost an equal number die in the first month of life. These deaths are due in large measure to lack of adequate care of the mother during pregnancy and at delivery and of mother and infant during the postnatal period.

Experience has shown that piecemeal effort — a prenatal clinic or a public-health nurse here and there — is not sufficient to reduce this wastage in human lives. What is needed is for every expectant mother to be under the supervision of a good physician during the prenatal period, and to receive proper service at delivery and adequate medical and nursing attention for herself and her baby thereafter. It is the proposal of the committee that the funds to make this possible be made available to state and local agencies.

Mental Disease. An estimated total of 500,000 persons are in hospitals for mental disease. The mentally diseased and defective demand more than twice the volume of hospital and institutional care required of all other diseases combined. In 1934 all but 2 per cent of patients in hospitals for mental disease were in public institutions; approximately $150,000,000 is expended annually for their care. Known methods are far from being fully utilized for the prevention, treatment and supervision of the mentally diseased and deficient.

These are but a few examples, briefly presented, of the public-health problems with which we are confronted, but perhaps they will suffice to show the need for doing something more than has been done. It is possible by applying the knowledge

of public health now available to cut down greatly the economic losses these and other diseases entail. The plan which the committee recommends is in substance as follows:

A. The development of state and local health organizations to a degree that will enable them to apply more generally and effectively public-health measures for the prevention of disease and the promotion of health.

In view of the excellent beginning already made in carrying out health activities under the provisions of the Social Security Act, it is recommended that federal participation in state and local health services be extended through additional grants-in-aid to the states. Increasing federal participation and leadership should promote the inauguration and expansion of fundamental and accepted health services, and the extension of newly developed services under state and local operation and control. Special effort should be directed toward those diseases which are important causes of sickness and death and against which we already have effective measures of proved value: tuberculosis, venereal diseases, pneumonia, cancer, malaria, mental diseases and occupational diseases.

B. The expansion of the work already carried on under the provisions of the Social Security Act for health services to mothers, children and crippled children.

It may be possible to save the lives of 70,000 mothers and babies each year if means are made available. There are 90,000 deaths a year of children under fifteen. Note that the work is done through the state and local health agencies of the several states in accordance with the laws of each.

MEDICAL CARE FOR THE MEDICALLY NEEDY

The need for medical care of persons on relief and in families with very low incomes is completely recognized by the medical profession, by public-health and welfare authorities and by others. While death rates are higher and sickness more frequent and severe among the poor than among families in comfortable circumstances, the poor receive less medical care than the well-to-do. There is not a state in the nation, and scarcely a county or city, that has not been confronted with this critical problem. Yet the present system of public medical care has failed to meet this situation.

It is estimated that 40,000,000 persons — almost one third of our population — are today in families with incomes of less than $800. Half this group are dependent on public funds for food and shelter. The other half — the so-called self-supporting families — can provide a minimum of food, clothing and shelter for themselves, but cannot meet their sickness costs. A family in this latter group may go along for months without applying for relief. Then the bread-winner becomes sick, and income, precarious as it is, stops. The family is on relief. Or again, a mother contributing to the support of the family may have to give up her job to care for a sick child or husband, and so the family goes on relief. A large proportion of such needy people live in small cities or rural areas in which there are few hospitals, doctors and nurses. This is a major obstacle to their efforts to obtain adequate medical care.

Local governments have proved unequal to the solution of such problems without assistance. It is the proposal of the committee, therefore, that state programs aided by the federal government be developed as the only adequate solution for the needs for medical care of this large group of the population. Public funds in addition to those now expended are necessary to pay for physicians' fees, drugs and appliances, hospitalization and nursing care and essential dentistry. The committee recommends that the programs be organized on a state and local basis, with the full cooperation of the medical profession and of public and private hospitals and clinics, health departments and welfare agencies. No uniform program is proposed to meet the varying needs of the states. Indeed, the proposal for medical care of the poor is founded on the belief that, given necessary financial and technical aid, every state will be able to work out a satisfactory way whereby its sick poor will receive an approved standard of medical care, the costs of which, including doctor's services, are paid from public funds.

EXPANSION OF HOSPITAL FACILITIES

The development of any program designed to provide medical services to meet the needs of large groups of people involves a consideration of existing hospital facilities. The second recommendation of the committee therefore relates to the expansion of hospital facilities. It embraces a plan for providing essential hospital beds and facilities with such geographic distribution that they will be within reasonable distance and at reasonable cost so that the great majority of our people who need them can use them. It is proposed to add 360,000 beds to the million now found in registered general hospitals, tuberculosis sanatoriums and mental institutions. In addition, the committee proposes the construction and equipment of at least 500 diagnostic centers in remote areas where it would be impracticable to construct hospitals. These could also serve as headquarters for local health departments, thus co-ordinating the health services of the community. Through these

centers, as well as through the proposed expansion of hospital facilities, physicians hitherto handicapped by lack of adequate diagnostic equipment and laboratory services would be able to render better service to their patients.

It is not planned to build a new hospital in every county in the United States. The committee simply proposes to aid the states in increasing the number of free and low-cost beds in general hospitals in communities where they are needed, and to relieve the already overcrowded conditions in tax-supported institutions for the care of the tuberculous and the mentally ill. This may be done either by building new institutions or by adding to approved hospitals. In its program for the expansion of hospital facilities, the committee considers the country as a whole with its varying social, economic and geographic conditions. The estimate of 360,000 additional beds and 500 diagnostic centers, with temporary maintenance grants for the support of the new beds, represents a measure of need on a national basis which must be subdivided to ascertain local requirements.

GENERAL PROGRAM OF MEDICAL CARE

The fourth major problem to which the committee has given consideration relates to the financial burdens and the economic insecurity which sickness creates for self-supporting persons. I do not believe that anyone knows all the answers to the problems of general medical care, nor does the committee assume this position. Nevertheless, sufficient experience has been gained in other countries and in the operation of many plans now under way in different parts of the United States to warrant planning for a more even distribution of the costs of medical care in this group.

No one can say whether your family or mine will get through the next year without a catastrophic illness. Self-supporting families can ordinarily meet the costs of minor sickness, but often they are unable to cope with a prolonged, serious illness. For the vast majority of our people, such a catastrophe often spells an insupportable burden of debt, even of serious curtailment of income and of financial disaster. The committee recommends that federal aid be given the states so that they may develop plans for distributing this unpredictable and disastrous burden of illness in families in moderate circumstances. Two ways — or a combination of the two — are suggested. The first is to finance medical care for the entire population through a general tax. The second relates to self-supporting families only, and involves the application of the insurance principle. A scheme of compulsory health insurance, aided in part by the federal government, would require contributions by the insured. Since it would be difficult if not impossible to apply the insurance principle to a numerous group of the population, namely agricultural workers, domestic labor and of course the unemployed, it might be necessary for some states to adopt a combination of these two methods.

It should be borne in mind that the committee at no point in this program suggests a national compulsory health-insurance plan or any mechanism for the rendering of medical care which would call for federal or state regimentation of medical practice. The road is left open to every state and every community to work out a satisfactory way by which medical care may be purchased without hardship. Federal participation would be confined to financial assistance and technical aid in developing the program.

INSURANCE AGAINST LOSS OF WAGES DURING SICKNESS

The fifth recommendation of the committee contemplates a plan of compensation for loss of wages because of sickness. The principle of this program is written into the law of virtually every state in the Union in workmen's compensation provisions. It is proposed that the federal government take the leadership in extending this principle to cover loss of wages resulting from general illness, as well as sickness resulting from employment. In view of the fact that not only the costs of medical care but the loss of income during disability is a principal factor in dependency — in good times and in bad — this proposal is both reasonable and sound.

COSTS OF THE PROPOSED PROGRAM

What will this vast program cost, and who will pay for it? It should be stated that the committee made no estimates for the costs of the last two recommendations, since these proposals deal primarily with suggestions for the redistribution of over-all expenditures now being made. The estimated costs of the first three proposals are governed by the principle of effective, comprehensive, long-range planning. A gradual development of the needed facilities and services over a ten-year period is contemplated. Effectively to establish adequate public-health service, maternal and child-welfare programs, medical care of the needy and expansion of hospital facilities, a maximum estimate of $850,000,000 annually in funds from federal, state and local governments was made. Of this sum the federal government would pay on the average about 50 per cent.

Estimates for preliminary stages of the program were made for certain of the proposed activities, as:

Recommendation I-A (public health). For the first year, $20,000,000 from federal, state and local sources, with gradual increases to a possible maximum of $200,000,000 by the beginning of the seventh year.

Recommendation I-B (maternal and child health). For maternity and infancy, during the first year, $9,000,000, with gradual increases to $50,000,000 in the fifth year, and to the full amount, $95,000,000, in not less than ten years. For medical care of children, during the first year, $6,000,000; $30,000,000 by the fifth year; and not less than $60,000,000 by the tenth year, provided that Recommendations II and III are not in full operation at that time.

Recommendation II (hospital facilities). The total overall cost is estimated at $1,104,500,000 for construction, plus $177,000,000 in federal grants for temporary maintenance, or an average annual expenditure of about $146,000,000 for ten years.

Recommendation III (medical care for the medically needy). For the first year, $50,000,000; by the fifth year, $150,000,000; by the tenth year, $400,000,000.

Thus, in the first year it is estimated that approximately $150,000,000 would suffice to launch sound, well-planned programs in these directions.

Federal participation would amount to 50 per cent of the total expenditure, with the exception of temporary maintenance grants for hospital facilities which would be borne in whole by the federal government.

* * *

Our experience with the administration of the public-health provisions of the Social Security Act has shown the effectiveness of federal and state co-operation in the development of sound programs of service and health conservation. Plans for the work to be accomplished are initiated in the state health departments. Administration and control of the activities carried on in the states remain in the hands of state and local authorities. The function of the federal government is to level the inequalities in financial resources in the states, and to provide the technical and consultant leadership essential in a well-co-ordinated national attack on preventable sickness and death.

These principles are suitable for immediate application in a far-reaching and comprehensive program for the health protection and medical care of our people. Indeed, it is suggested that the administrative procedures worked out by the states with the federal government in the development of the health provisions of the social-security program be used as a guide for future expansion.

The committee confidently expects from such a program a generous return on the investment. The question, from the business standpoint, is not, Can we afford a national health program of sufficient scope and extent to meet the needs, but rather, Can we afford not to do all that can be done to reduce needless sickness and death?

THE CHANGING PRIVATE PRACTICE OF MEDICINE*

ROGER I. LEE, M.D.

BOSTON

IT is always a pleasure and privilege to listen to Warren Draper. He talks our language. It could hardly be otherwise since he received his formal education at Amherst and at the Harvard Medical School. But it is the man himself that catches our imagination and holds our admiration. To his formal education he brings humor, intelligence, sincerity and devotion. His experience, since his academic days, has been vast, and what he says is authoritative.

We shall all agree, I think, that in the last few years there has been a tumult and a turmoil about what seems to be designated at this moment as "socialized medicine." It appears to be the same thing that was once called the "cost of medical care," then later the "costs of medical care," and that eventually turned out to be none of these or even the "costs of sickness," which it might be argued was what was really meant. At this phase the doctors contributed a phrase "medical economics" which was the worst term yet in its implications and possible interpretations. Perhaps socialized medicine is a good term. I do not know. But I do know that sociology is to many people the study of socialism. At this moment nearly everyone who has a pen or a voice has taken part in the excitement, and everyone has his theory. "State medicine," "compulsory health insurance," "adequate medical care for all," "medical care a right not a privilege" are phrases on the tip of everybody's tongue. Sociologists, reporters, economists, sob sisters, politicians, hospital superintendents, all want to reorganize the medical profession.

But the medical profession is not having a private row of its own. There is the Alberta Plan, the Thirty-Dollars-Every-Thursday, alias the Ham-and-Eggs, Plan, and countless others. Everyone has his plan. It reminds one of the hurricane. Everyone wanted to tell his hurricane experi-

*An address delivered at the New England Postgraduate Assembly, Cambridge, November 15, 1938.

ence. We need a device like that of the sandwich man who on the bottom of his boards had printed "I'll listen to your hurricane story for ten cents." I, for one, am prepared to believe that most of these plans are devised by honest, sincere people. But experience leads to a certain cynicism. For example, I recall that all the noted economists, with rare exceptions, if any, declared that the World War could only last two months or a few months at most. I also recall that, with few or no exceptions, none of these economists predicted the so-called depression. Yet it is a fact that the World War lasted over four years, and that there was a depression — somehow doctors survived both, which is more than can be said of many of our best businesses.

At the National Health Conference held in Washington last summer, the comment of one man that "the plans were too simple to be reliable" merits careful consideration.

I* have elsewhere pointed out the obvious fact that rapid changes are taking place in medical practice. Those changes are all in the direction of socialized medicine and state medicine. I have watched in the hospital the birth and growth of social service. I have watched the birth — in the same sense that Philadelphians always say that Benjamin Franklin was born in Philadelphia at the age of seventeen — of the United States Public Health Service and, again parenthetically, I am a member of its advisory council. During long years of service on the Massachusetts Public Health Council, I have watched the growth of the state public-health activities. At no time have I believed that close, friendly co-operation between medicine and public health is an impossibility. But I have also watched the growth of the medical profession. I point out now what is often forgotten, that the public-health movement was a legitimate and "planned" child of the medical profession and has always been fostered and nurtured by it. And I also want to emphasize that the medical profession, essentially without assistance, corrected abuses and put education in medical schools on its present high plane. True it is that certain governmental units, such as the Commonwealth of Massachusetts, have disgraceful licensing laws. But that is a fault of the states, not of the profession. Again, the extraordinarily favorable morbidity and mortality statistics in this country are due to the medical profession.

Doubtless things have changed since the horse-and-buggy days, and even more since the doctor's-saddlebag days, and yet more since the gold-headed-cane days. Personally, I like to think of the doctor using the gold head of the cane as something to put in his mouth because he knew so little in those days that any utterance of his might expose his ignorance. But, there is ignorance in these days. There were charlatans then as there are now. Human nature has not changed. (Indeed, it might be argued from some of the events in this troubled world that human nature is worse.)

As I see it, the problems of medical practice are essentially only two: that of the distribution of medical services and that of continuing the education of the practicing physician.

So far, the bulk of the emphasis has been laid on distribution. Formerly, the doctor took rich and poor in his stride. One of the most successful general practitioners has told me that he never charged a servant, a minister, a doctor or a nurse. And there were many others that he did not charge. It is to the credit of the medical profession that the impetus to make professional charges for care of the indigent did not come from its ranks. Yet it is an old custom. The young doctor was the city or town physician or was paid a small sum yearly for work in the districts of the Boston Dispensary. He did that to keep his hand in, if you will, but also to help out his budget, — accursed word of modern times, — just as he examined for insurance companies, and the like. Nowadays there seems to be an agreement that the doctor should not carry, without help or without some plan, the whole or nearly the whole of practice among the indigent. And within the hospitals, the administrators see possibilities of balancing their budgets from reimbursements for the care of indigent patients.

Your doctor of today must give much of his time and energy to keeping himself abreast of that swiftly running stream of medical progress. The same friend to whom I referred earlier did his own social-service work, and he did it marvelously well. But that too is largely given up by the practicing doctors. This is an age of specialism. Even if we grant, and I think we must, that specialism has gone too far, we must acknowledge that the public likes the idea of specialists (except the idea of paying for them) and that specialism has become a sort of legitimate showmanship that somehow gets by the committees on ethics and discipline. Regardless of this, the practitioner who keeps himself in touch with medical advances is going to be a better, a more skilful doctor. In most cases he is not going to be the family friend, except on the golf links or at the bridge table. To be sure, this is a conservative view because many of our planners would have him a servant of the government. And this, I fear, would result in many doctors becoming a

*Lee, R. I.: The rights and lefts of medical practice. New Eng. J. Med. 218:107-109, 1938.

part of a great bureaucracy. But much more dismal than that picture is one of two great groups of practicing doctors, side by side and in competition. On the one hand, one might envisage the government, let us say the United States Public Health Service, developing and extending its practice of medicine. Of course, the beginnings would be small—the indigent, supposedly far-off areas, rural hospitals, and so forth. Is it likely or reasonable to suppose that these several hundred diagnostic clinics will be exclusively diagnostic? Who can differentiate precisely where diagnosis leaves off and treatment begins? Then let us remember the story of the camel and the tent. In my opinion such a situation would be indeed a calamity, but it is by no means fantastic.

I believe that if the doctors and the medical profession continue their consecration to the ideals and traditions which have brought forth such an abundant harvest in relation to the welfare of all the people, such changes as are necessary will be adopted now and in the future just as they have been in the past. Your 1938-model doctor hardly resembles his father, but medicine is still a glorious profession. It is not a trade, nor a political football and, please God, it will never be.

And in the end we will look on the glorious achievements of the past and present and say with justifiable pride, I shared, perhaps humbly, in some of these achievements. We have been through a war and through a depression, but we still have our profession.

264 Beacon Street.

THE CHEMISTRY OF THE ANAEROBIC RECOVERY OF MUSCLE*

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IN THE course of the last fifteen years a great deal has been accomplished in the elucidation of the chemistry and thermodynamics of the processes which underlie muscular activity. Although the final goal, the understanding of the physical mechanisms of contraction and the interrelations of the various chemical processes, is as yet remote, the significance of the endothermic and exothermic reactions is gradually becoming clear.

In this report I shall discuss that portion of the process which is concerned with the events of the anaerobic-recovery phase of muscular contraction. Up to 1926, as is known, a study of muscle under anaerobic conditions revealed only the relation between muscular activity and the formation of lactic acid. Subsequently, two more chemical reactions were recognized which had both causal and temporal relations to the performance of work. One was the discovery that the "phosphagen" (Eggleton and Eggleton[3]) in muscle was creatinephosphate (Fiske and Subbarow[5, 7]), which was capable both of decomposition into creatine and phosphate and of resynthesis into the original compound. The other was the discovery in 1929 of adenylpyrophosphate (adenosinetriphosphate), which can hydrolyze into adenylic acid (adenosinemonophosphate) and phosphate (Lohmann[13, 18] and Fiske and Subbarow[6]). These split products can then be resynthesized, with the intermediary formation of adenosinediphosphate, into the original compound.

This hydrolysis of and esterification to adenosinetriphosphate constitutes a necessary step in the reaction that Embden had interpreted as the breakdown and synthesis of "lactacidogen" (the preformed hexosephosphate of muscle). Finally Lundsgaard,[16–18] in 1930, discovered that a muscle poisoned with iodoacetic acid could contract anaerobically for some time, entirely without the formation of lactic acid. Such important discoveries rendered the former concepts so inadequate that my friend A. V. Hill[9] in 1932 gave a series of lectures in America under the title "The Revolution in Muscle Physiology."

Such revolutionary periods are always fertile epochs. Although in the beginning some confusion of opinion may arise, and some doubting scientists may be ready to distrust and discard all the data, there gradually emerges a more clearly defined concept. This is especially true when the previous data are found to reinforce the new and permit the integration of the whole. The accumulation of new facts warrants such a formulation at present with regard to the processes of the anaerobic recovery of muscle.

The suspicion of contemporary scientists concerning the validity of our picture is based on two objections. (1) Do the chemical analyses of dead muscle, in which splitting and synthesis of the chemical compounds had been found, give a reliable picture of the events in vivo? Are they not

*A lecture delivered before the Alpha Omega Society, Harvard Medical School, October 29, 1937.

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artefacts, postmortem changes, whose relation to vital processes is unknown? (2) When three different and apparently unconnected processes are already known to accompany muscle activity, have we not to assume many others, and might it not be that none of the processes known so far are of especial importance in muscular work?

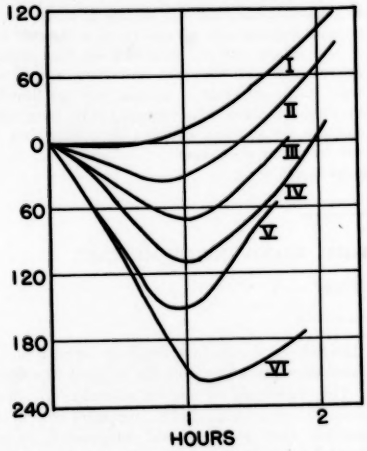


Figure 1. *Hydrogen-Ion Concentration Changes in Muscle during Fatigue as Measured by Carbon-Dioxide Exchange.*

Carbon-dioxide output — indicating increased acidity — is measured on the ordinates from zero upward: carbon-dioxide uptake — indicating increased alkalinity — is measured on the ordinates from zero downward.

Curve I. *1.1 vol. per cent (pH 7.93).*
" II. *5.0* " " " (" *7.23).*
" III. *7.9* " " " (" *6.97).*
" IV. *16.2* " " " (" *6.75).*
" V. *34.5* " " " (" *6.45).*
" VI. *71.5* " " " (" *6.07).*

I believe that both objections can be confidently refuted. In respect to the first, it was learned some years ago that the syntheses and decompositions in question were accompanied by changes which could be demonstrated in the living muscle by physicochemical measurements. For example, the alterations connected with the decomposition of creatinephosphate are always contrary to those connected with the breakdown of carbohydrate to lactic acid. Thus Lipmann and I[12] in 1930 found a shift of pH to the alkaline side with the enzymatic splitting of creatinephosphate, and to the acid side with the formation of lactic acid. On account of the difference between the second dissociation constant of phosphoric acid and that of creatinephosphoric acid, the alkalinization connected with this breakdown became the greater the more the initial pH was brought to the acid side by the addition of carbon dioxide. Chemical analysis showed that, on anaerobic stimulation of a normal muscle, at first much creatinephosphate was broken down compared to the amount of lactic acid formed; with increasing fatigue this proportion was shifted so that an increase in the formation of lactic acid resulted. Moreover, the amount of creatinephosphate present was the resultant of the simultaneous breaking down and resynthesis, and hence the amount of the creatinephosphate split was less during recovery than at the height of tetanus. The conclusion is that during a contraction the rate of breakdown corresponds to the development of tension, but that

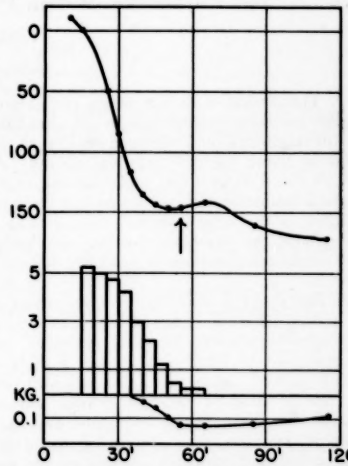


Figure 2. *Changes Accompanying Fatigue in a Muscle Poisoned with Iodoacetic Acid.*

The upper curve represents the carbon-dioxide uptake (cu. mm. per gram of muscle) in an atmosphere containing 33 vol. per cent carbon dioxide. The rectangles represent the sum of tension of twitches per gram of muscle during 5-minute intervals. The lower curve represents the tension of rigor per gram of muscle.

the resynthesis is incomplete with the first contractions, while in the latter ones the resynthesis is more and more complete, so that in the steady state no further breakdown can be observed.

The change in pH of the living muscle during

fatigue corresponds exactly to that predicted by chemical analysis. In a series of contractions, the muscle becomes at first more alkaline and later more acid, and the alkalinity is the more pronounced the higher the concentration of carbon dioxide (Fig. 1). In muscle poisoned by iodoacetic acid (Fig. 2) the alkalinity increases with fatigue. Chemical analysis proves that the hydrolysis, which is the equilibrium between breakdown and resynthesis, is as large as in normal muscle. However, at the height of tetanus and subsequently there is no resynthesis of creatinephosphate or formation of lactic acid. Recently Dubuisson[2] measured this pH shift with a glass electrode and thus obtained still more exact results. When the pH is calculated from chemical data in the poisoned muscle, the agreement between prediction and measurement is almost exact. In the normal muscle the formation of lactic acid is smaller than that calculated from the change in pH, but is still in essential agreement with that predicted.

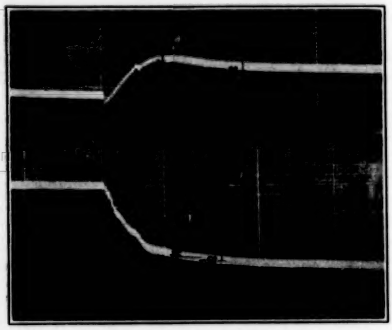


Figure 3. *Volume Change in a Series of Tetanic Contractions of 2 Seconds' Duration.*

The upper curve represents normal muscle undergoing fatigue, and the lower iodoacetic-acid-poisoned muscle. The distances between the two arrows on each curve designated W *give the corrections for the heat of contraction. The distances between the two arrows designated* M *give the total volume changes per gram of muscle after complete fatigue.*

Other physicochemical measurements also indicate that antagonistic effects are produced simultaneously in muscle. As I found with Möhle[22] the molecular volume rises when glycogen is split to lactic acid; it decreases with the splitting of creatinephosphate and also of adenosinetriphosphate. Besides the rapid volume change, discovered by the Hungarian investigators Ernst and Üj,[1] a more protracted one can be observed, which is co-ordinated with chemical reactions. I disregard here the course of the details of the change in volume during single tetanic contractions, and give only two curves which show the total effect. Normal muscle undergoing fatigue (Fig. 3) shows at the onset a diminution in volume which accompanies the initial breakdown of creatinephosphate. This decrease is followed by an increase in volume which parallels the excess formation of lactic acid. In muscle poisoned by iodoacetic acid, the diminution in volume is present from the onset, and the shrinking continues until the development of rigor (Meyerhof and Möhle[22]). In regard to volume changes also, the muscle treated with iodoacetic acid shows agreement between calculated and determined values to be almost exact; yet in the normal muscle the effect of lactic acid is smaller than the calculated value, but qualitatively in substantial agreement with the theory.

A study of the changes in transparency of muscle has been made at our institute by Muralt.[24] It will suffice to state that he found that these changes in the muscle corresponded to those predicted from the observed chemical reactions.

We may conclude without reservation that the splittings and resyntheses revealed by chemical analysis really take place during muscular activity.

Experiments on living muscle have demonstrated that a breakdown of creatinephosphate precedes the formation of lactic acid. Therefore the energy of the latter is available for the endothermic resynthesis of creatinephosphate. Thermodynamic calculations on normal muscle and that treated with iodoacetic acid correspond with this conception. The more exact elucidation of this relation was due to experiments on the extracts of muscle containing the enzymes. Although such an experiment bears no relation to the events taking place in muscular activity, the chemical reactions can be studied with excellent results. The transformations in energy of these reactions, which are catalyzed by enzymes, calculated per mol, are shown in Reactions *A* and *B*.

A ½ hexosediphosphate → 1 lactic acid + 1 phosphate + 16000 cal.
heat of neutralization in muscle = + 8000 cal.
+ 24000 cal.

B creatinephosphate ⇄ creatine + phosphate + 11000 cal.

The values given are those for total energy, which do not coincide with the free energies but do correspond to the myothermic measurements. The heat of splitting of hexosediphosphate into lactic acid and phosphate amounts to 16,000 calories per mol of lactic acid; but in muscle this heat is increased by the neutralization of lactic acid to about 24,000 calories. On the other hand, the splitting of one mol of creatinephosphate yields 11,000 calories. Very careful experiments by Lundsgaard[18] have shown that during the anaerobic restitution two mols of creatinephosphate are resynthesized for each mol of lactic acid formed after contraction. Thus + 24,000 calories for one mol of lactic acid formed is opposed to — 22,000 calories for two mols of creatinephosphate resynthesized, so that a slight evolution of heat results.

The well-known measurements of Hartree[8] and Hill[9] have proved that a very small amount of delayed heat is liberated during anaerobic restitution, averaging 5 per cent of the initial heat. The amount is less when the muscle is in good condition. Moreover, under special conditions a transitory endothermic phase has been observed at the beginning of the anaerobic restitution. This phenomenon will be referred to later. Lohmann and I found ten years ago that, in an extract of muscle also, creatinephosphate is resynthesized from its split products during the formation of lactic acid. Some years later we[21] observed that the addition of adenosinetriphosphate to a muscle extract caused synthesis of creatinephosphate. Later Lohmann[14] demonstrated that the reverse reaction, namely the splitting of creatinephosphate, caused the synthesis of adenosinetriphosphate. It was therefore obvious that a reversible reaction takes place, as illustrated in Figure 4. The existence of this reaction was proved by Lehmann[11] at our institute. The pH has a great influence on this equilibrium; the amount of creatinephosphate increases with the alkali.

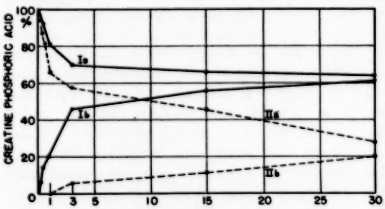


Figure 4.

adenylic acid + 2 creatinephosphate ⇄ adenosinetriphosphate + 2 creatine.

Curve Ia *starts from the left side of the equation; Curve* Ib *from the right. Curves* IIa *and* IIb *show the same reaction with excess of creatine.*

C	adenylic acid + 2 creatinephosphate ⇌ adenosinetriphosphate + 2 creatine +	0 cal.
D	adenosinetriphosphate → adenylic acid + 2 phosphate +	24000 cal.
E = C+D	2 creatinephosphate ⇌ 2 creatine + 2 creatine + 2 phosphate +	22000 cal.

This reaction is summarized in Reactions *C, D* and *E*. Thus 24,000 calories from splitting adenosinetriphosphate is to be compared with 22,000 calories from the splitting of two mols of creatinephosphate, so that the actual heat of the reversible Reaction *C* is almost zero. If, now, creatinephosphate is to be split into creatine and phosphate, Reaction *C* has to go to the right; the adenosinetriphosphate has then to be converted into adenylic acid and two mols of phosphate by the action of phosphatases (*E = C + D*). The removal of adenosinetriphosphate (Reaction *D*) causes Reaction *C* to go from left to right, and results in a splitting of creatinephosphate. The removal of adenylic acid causes the reaction to go from right to left, and synthesizes creatinephosphate.

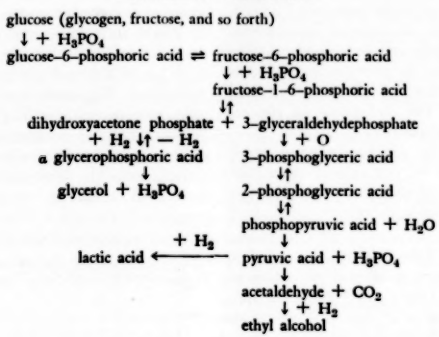
This intermediary action of adenylic acid is brought about by the formation of lactic acid in two different ways, with a resultant shift in the equilibrium toward the synthesis of creatinephosphate. To explain this more fully I must briefly describe the sequence of intermediary products of the breakdown of carbohydrate, which in the formation of lactic acid and in alcoholic fermentation are almost identical. The steps involved are indicated diagrammatically in the accompanying scheme. The detailed proof of their validity (Meyerhof, Kiessling, and Schulz[20]) is omitted.

Pyruvic acid may be the starting-point for the formation of either alcohol or lactic acid. In the latter case we have the reduction of pyruvic acid into lactic acid. In the stationary state this reduction reaction is equivalent to the oxidation of triosephosphoric acid into phosphoglyceric acid. The reversible reactions designated by double arrows progress without coenzymes, whereas phosphorylation and hydrogen transfer require coenzymes. The coenzyme for phosphorylation is the adenylic system; that for hydrogen transfer is the cozymase discovered by Harden, studied by Euler and chemically determined by Warburg.*

*References to this subject may be found in the article by D. Needham in the *Annual Review of Biochemistry*, 1937.

In 1934 Parnas and his associates[25] discovered that phosphopyruvic acid, in both muscle tissue and extracts, on splitting does not set free inceeded in solving this puzzle. Because the splitting of phosphopyruvic acid is the only source of phosphate in these reactions, the synthesis of the

BREAKDOWN OF CARBOHYDRATE



organic phosphate, but transfers it to creatine to form creatinephosphate. This is represented in Reactions *F*, *G* and *H*. The adenylic system, second mol of creatinephosphate cannot be derived from this source. It will now be shown how the second mol of creatinephosphate is

PARNAS REACTION

F	2 phosphopyruvic acid + adenylic acid → 2 pyruvic acid + 1 adenosinetriphosphate
G	1 adenosinetriphosphate + 2 creatine ⇌ adenylic acid + 2 creatinephosphate
H = F+G	2 phosphopyruvic acid + 2 creatine → 2 pyruvic acid + 2 creatinephosphate

which acts as a catalyzer, does not figure in the end result ($H = F + G$). The splitting of phosphopyruvic acid is an intermediary reaction of the formation of lactic acid also, for one mol of lactic acid and one mol of phosphocreatine are produced for each mol of phosphopyruvic acid hydrolyzed.

The analysis is, however, not yet complete, for as previously stated, two mols of creatinephosphate are synthesized by muscle for each mol of brought about by hydrogen transfer.

Exactly as the adenylic system acts as a catalyzer of phosphate transfer, so cozymase interacts as a catalyzer of hydrogen transfer. According to Warburg and Christian,[27] cozymase is a pyridinenucleotide which takes up hydrogen according to the equation:

pyridine + H_2 → dihydropyridine

Experiments at our institute (Meyerhof[19]) show

I	triosephosphoric acid + pyridine → phosphoglyceric acid + dihydropyridine
J	dihydropyridine + pyruvic acid → pyridine + lactic acid
K = I+J	triosephosphoric acid + pyruvic acid → phosphoglyceric acid + lactic acid
L	triosephosphoric acid + pyridine + adenosinediphosphate + phosphate → phosphoglyceric acid + dihydropyridine + adenosinetriphosphate
M	adenosinetriphosphate + creatine → adenosinediphosphate + creatinephosphate
N = J+L+M	triosephosphoric acid + pyruvic acid + phosphate + creatine → phosphoglyceric acid + lactic acid + creatinephosphate

lactic acid (see Reactions *A* and *B*). But the Parnas reaction yields only one mol. How does the synthesis of the second mol of creatinephosphate come about? Only recently have we succeeded in solving this puzzle. Because the splitting of phosphopyruvic acid is the only source of phosphate in these reactions, the synthesis of the second mol of creatinephosphate cannot be derived from this source. It will now be shown how the second mol of creatinephosphate is brought about by hydrogen transfer.

Exactly as the adenylic system acts as a catalyzer of phosphate transfer, so cozymase interacts as a catalyzer of hydrogen transfer. According to Warburg and Christian,[27] cozymase is a pyridinenucleotide which takes up hydrogen according to the equation:

pyridine + H_2 → dihydropyridine

Experiments at our institute (Meyerhof[19]) show that the hydrogen transfer in the formation of lactic acid takes place according to Reaction *K* of the accompanying scheme. Reaction *I* proceeds very slowly by itself, and consequently also Re-

action *K*. However, if inorganic phosphate and adenylic acid or adenosinediphosphate are present, the reaction goes rapidly. Under these conditions the approximate Equation *L* is valid. This is followed by the rapid reaction represented by Equation *J*. The adenosinetriphosphate formed according to Equation *L* is reconverted into adenosinediphosphate according to Reaction *M*. At the same time the creatine is phosphorylated, thus providing for the formation of the second mol of creatinephosphate. The end result of the reaction is given in Equation *N*.

The adenylic and the pyridine systems serve only as catalyzers and do not appear altered in the final reaction. Rapid oxidation and reduction take place between triosephosphoric acid and pyruvic acid. For each mol of lactic acid formed one mol of creatinephosphate is synthesized from creatine and inorganic phosphate. The energy from the oxidation-reduction reaction is utilized for the synthesis of creatinephosphate.

Table 1. *Total Balance.*

1 hexosediphosphate + 4 creatine + 2 phosphate → 2 lactic acid + 4 creatinephosphate
32000 cal. — 44000 cal. = —12000 cal.

Components	1 Cc. Muscle Ext. Contains $\times 10^{-4}$ mol	Ratio	Found	Calculated
A Hexosediphosphate	—15.5			
B Inorganic phosphate	—28	B/A	1.75	2
C Creatinephosphate	+60	C/A	3.90	4
D Lactic acid	+24	D/A	1.55	2

The energy balance for all these reactions has not only been calculated but has also been measured calorimetrically. The heat evolved from the splitting of sugar to lactic acid, without counting the heat of neutralization, is + 16,000 calories per mol. The heat of splitting phosphopyruvic acid into pyruvic and phosphoric acid is + 8000 calories. In the Parnas reaction this + 8000 calories is to be balanced against — 11,000 calories from the synthesis of one mol of creatinephosphate, so that the complete reaction has a negative heat of 3000 calories. Therefore of the total heat incident to the formation of lactic acid, + 16,000 calories, half is accounted for by the splitting of phosphopyruvic acid. There remains only half the total heat for the sum of all the other reactions which result in one mol of lactic acid. This heat is the result of different components with opposite signs. When we disregard the sources, 8000 calories is available for the synthesis of the second mol of creatinephosphate, although 11,000 are required.

The total changes may then be summarized as follows. When we convert hexosediphosphate, in a suitable enzyme extract, in the presence of creatine and phosphate, taking into account the Parnas reaction and that described above, we can calculate and measure the total energy transfers, as shown in Table 1. Four mols of creatinephosphate are synthesized from one mol of hexosediphosphate and two mols of inorganic phosphate. In Table 1 are given the actual figures of an experiment in which the energy transfer is calculated in terms of 10^{-4} mol per cubic centimeter of muscle extract. For example, 60×10^{-4} mol of creatinephosphate is synthesized from 15.5×10^{-4} mol of hexosediphosphate. The ratio found is 3.9 instead of the calculated ratio 4.0 (Meyerhof, Schulz, and Schuster[23]). The formation of two mols of lactic acid is strongly endothermic (−12,000 calories).

As an example of the rates involved in this reaction, two calorimetric measurements are given in Figure 5. In the one case neutralization was effected by sodium bicarbonate and in the other by ammonium bicarbonate. With the former the total reaction is endothermic because the heat of neutralization is small. The temperature falls rapidly at first, and then more slowly. Neutralization with the latter gives values similar to that of protein. The initial negative heat phase is followed by a positive heat neutralization and the total is slightly positive. This curve resembles that for the heat of the anaerobic restitution of muscle as found by Hartree[8] when working under especially suitable conditions. I think that these calorimetric measurements in enzyme extracts render a most perfect analogy to the rate of heat production in the anaerobic restitution of living muscle.

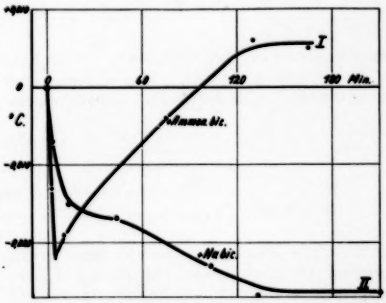


Figure 5. *Course of the Heat of Reaction (Meyerhof*[19]*).*

Curve I *in presence of ammonium bicarbonate shows great heat of neutralization; Curve* II *in presence of sodium bicarbonate shows small heat of neutralization.*

These peculiar reactions are of great significance in the metabolism of living muscle. The presence

of free creatine and free phosphate during the formation of lactic acid by the muscle enzymes is important not only for the thermodynamics of the reaction but also for its velocity. As is well known, hexosediphosphate is decomposed slowly; a phenomenon which has prevented many investigators from considering this compound as a precursor of lactic acid or alcohol. In fact the triosephosphate originating from hexosediphosphate reacts very slowly in an enzymatic system with cozymase. However, this reaction becomes rapid as soon as inorganic phosphate, as an acceptor, and a little adenylic compound, as catalyzer, are present. In alcoholic fermentation the phosphate acceptor is glucose, but in muscle it is the very creatine which immensely accelerates the reaction. This sequence is graphically presented in Figure 6:

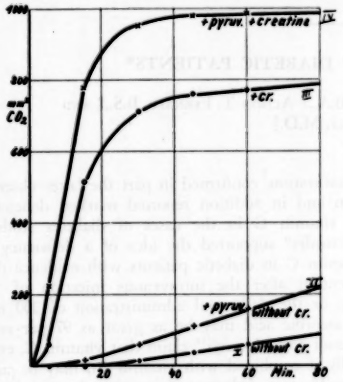


Figure 6. *Creatine Effects.*

Effect of creatine on the velocity of the breakdown of hexosediphosphate (Curves I *and* III*) and of the reaction between pyruvic acid and triosephosphate (Curves* II *and* IV*).*

for an enzyme extract with and without creatine, for the total breakdown of hexosediphosphate, and also for the reaction between pyruvic acid and triosephosphate. The increase in the velocity of the breakdown of hexosediphosphate by the coupling with the synthesis of creatinephosphate is of extreme significance in the kinetics of this reaction in muscle. In fresh muscle, only hexosemonophosphate is present in large quantities. It can be shown by special experiments that hexosemonophosphate reacts only after it has taken up one mol of phosphate and become hexosediphosphate, which is the general intermediary in the formation of lactic acid. So long as the muscle is resting, creatine is present as creatinephosphate and the lactic acid formation is minimal. But when muscle contracts, creatinephosphate is split into creatine and phosphate, and lactic acid is rapidly formed and released, as can be seen during the restitution period of muscle. This lactic acid induces the resynthesis of creatinephosphate as described above, and with the return to the original state, the formation of lactic acid ceases. By this means the total energy of carbohydrate breakdown is transferred to the resynthesis of creatinephosphate.

In muscle poisoned by iodoacetic acid the reactions can be similarly interpreted in so far as this coupling is concerned. Iodoacetic acid inhibits oxidation and reduction, and hence the triosephosphoric acid does not undergo any further reaction. Since there is no lactic acid, creatinephosphate which has been split cannot be resynthesized, because both kinds of phosphate transfer are lacking, namely the formation of phosphoglyceric acid and the splitting of phosphopyruvic acid. Anaerobically the free creatine remains unchanged. The free phosphate esterifies more glycogen, with the formation of hexosemonophosphate and hexosediphosphate. Apparently, as the experiments of Cori and his co-workers[1] and Parnas and Baranowski[26] have shown, this esterification of glycogen, as opposed to that of hexose, proceeds even without an oxidation-reduction reaction. Thus, when creatine is not available as a phosphate acceptor, the hexosemonophosphate and hexosediphosphate become the main products. The adenosinetriphosphate is preserved in the poisoned muscle so long as creatinephosphate remains. It breaks down only afterward, because the synthesis of adenosinetriphosphate is effected by the reaction of Lohmann[14] (see Reaction *D*), and ceases when this breakdown comes to an end.

The processes of the anaerobic restitution of muscle discussed here form only a small part of the chemical description of muscle activity. Many questions are as yet unanswered. Even the reactions here described require further elucidation. Especially requiring further study is the problem of why the simultaneous uptake of inorganic phosphate by the adenylic system accelerates the reduction of cozymase. In any event, it must be acknowledged that our understanding of the chemistry of muscle is considerably advanced over that of ten years ago. The older conception of the energy relations between the formation of lactic acid and the resynthesis of phosphagen can now be replaced by definite interdependent chemical reactions. By the elucidation of these reactions science has succeeded in at least partially unveiling one of life's fundamental processes.

Reprints of this article can be obtained from the Chemical Laboratory, Children's Hospital, Boston.

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THE VITAMIN C STATUS OF DIABETIC PATIENTS*

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THE physiological significance of vitamin C has become increasingly recognized since its identification as ascorbic acid[1, 2, 3, 4] and the adaptation of simple methods for its determination. Recently several investigators have reported an effect of vitamin C on diabetes and carbohydrate metabolism. Roller[5] in 1936 reported that the administration of vitamin C caused a diminution of the glycosuria in diabetic patients. He also observed a lessened rise in blood sugar during food-tolerance tests if 1000 to 3000 mg. of ascorbic acid was given with the food. In the same year Stoïcesco and Gingold[6] reported in normal individuals a fall in blood sugar following the intravenous injection of 240 mg. or the oral administration of 500 mg. of vitamin C. In diabetic patients the results obtained were variable. Similarly Stepp, Schroeder and Altenburger[7] reported a lowering of blood sugar in normal individuals following a single intravenous injection of ascorbic acid but no effect from oral administration. These authors also observed in normal individuals, but not in those with diabetes, an increased hypoglycemic action of insulin following the simultaneous injection of vitamin C and insulin. Pfleger and Scholl,[8] under different conditions of vitamin C saturation, confirmed in part the latter observation and in addition reported marked deficiency of vitamin C in the cases of diabetes studied. Schroeder[9] supported the idea of a deficiency of vitamin C in diabetic patients with evidence that retention after the intravenous injection of 150 mg. or the daily oral administration of 300 mg. of ascorbic acid may be as great as 97 per cent. Aszodi and Mosonyi[10] claim that vitamin C, especially if combined with vitamin B_1, may be used in mild cases of diabetes to supplant insulin. Their study is particularly interesting as it is based on the assumption that, since vagotonic effects are known to follow injections of vitamin C, there might well be a stimulation of the pancreas through the vagus, causing an increased insulin secretion. As evidence they show the lowering of the blood sugar of mice following an injection of either human or dog serum taken from a subject previously injected with vitamin C.

In contrast to the above evidence suggesting a more or less specific bearing of vitamin C on glucose tolerance, sensitivity to insulin and carbohydrate metabolism in general, are the completely negative findings of Kreitmair[11] and Armentano and his co-workers.[12] These authors deny any specific relation of vitamin C to diabetes.

The present paper deals with the vitamin C status of a representative group of diabetic patients under observation in the George F. Baker Clinic. The study is based on determinations of

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vitamin C in fasting blood plasma in conjunction with the saturation test proposed by Wright.[13] We hoped thereby to evaluate the adequacy of the average diet in use here, and to detect any significant deviation from the normal in the response were without fever or obvious signs of infection. These patients are referred to below as surgical cases.

The vitamin C content of the patients' diets prior to hospital admission was estimated by ques-

Table 1. *Vitamin C Values in Diabetic Patients.*

No.	Case No.	Age	Sex	Diabetic Condition			Vitamin C		Days in Hospital Before Test	Days After Operation	Data on Surgical Cases	
				Duration of Diabetes	Daily Insulin Dose*	Fasting Blood Sugar	Fasting Plasma Content	5-hr. Urine Excretion			Surgical Lesion	Operation
		yr.		yr.	units	mg. %	mg. %	mg.				
1	3649	56.3	F	15.3	16	0.16	0.33	65	13	10	3rd and 5th hammer toes, right foot.	Amputation, 3rd and 5th toes, right foot.
2	16878	70.1	M	0.4	4 + 24	0.13	0.42	322	11	8	Gangrene, left foot.	Left-thigh amputation
3	16887	61.8	M	0.9	10 + 24	0.08	0.47	362	4			
4	16926	62.5	M	14.9	10 + 20	0.10	0.52	401	6			
5	15261	63.8	M	13.4	16	0.09	0.53	446	2			
6	16266	68.3	F	12.9	16 + 10	0.16	0.56	404	13	12	Gangrene, right foot.	Right-thigh amputation
7	16765	38.6	F	0.9	24 + 36	0.23	0.56	458	4			
8	16901	61.6	M	27.9	12	0.14	0.66	386	2			
9	13022	68.6	F	4.3	14	0.21	0.66	397	4		Ulceration, right 3rd toe.	None
10	1877	55.6	M	18.4	10 + 28	0.11	0.66	406	13	11	Necrosis, left great toe.	Left-thigh amputation
11	15294	64.7	M	2.8	—	0.09	0.70	470	65	54	Carbuncle, left buttock.	Incision and drainage, left buttock.
12	16763	68.2	F	0.2	16 + 16	0.27	0.70	533	1			
13	12423	71.1	F	6.0	4 + 36	0.18	0.71	374	19		Infection, right great toe; ulceration, left great toe.	None
14	16986	68.8	M	>0.1	6 + 30	0.20	0.85†	—	20	12	Ulceration, right leg, heel and great toe.	Right-thigh amputation
15	16858	68.8	F	6.9	20	0.16	0.85	283	39	36	Gangrene, right great toe.	Right-thigh amputation
16	16868	21.8	F	5.5	10 + 48	0.07	0.85	305	5			
17	13612	46.8	M	21.3	16	0.06	0.85	618	2			
18	14021	63+	F	2.8	12	0.15	0.90	407	10		Necrosis, 4th toe, left foot.	None
19	16929	65.3	F	1.9	12	0.13	0.94	406	4			
20	16724	50.1	F	1.2	10 + 40	0.20	0.94	531	1			
21	16864	66.2	F	1.3	6 + 32	0.16	0.94	592	8	5	Varicose veins, right leg.	Ligation, right saphenous vein.
22	16712	60	F	8.3	16	0.08	0.94	750	4			
23	16897	68.2	M	0.1	24	0.13	0.99	288	12		Ulcer, left great toe.	None
24	6281	39.7	M	11.8	4 + 26	0.16	0.99	553	3			
25	16876	52.2	F	13.4	6 + 40	0.09	1.03	244	20		Infected corn, right great toe.	None
26	13821	39.9	F	15.0	14 + 20	0.09	1.03	504	1			
27	10673	57.8	F	12.8	20	0.20	1.03	559	11		Infected callus, right foot.	None
28	4295	60.7	F	23.8	6 + 28	0.07	1.03	580	5			
29	10356	41.4	M	6.9	24 + 40	0.09	1.03	622	5		Ulcer, left leg; abscess, right jaw.	None
30	16723	51.6	F	0.8	16	0.20	1.12	543	1			
31	16841	32.9	F	3.9	4 + 32	0.06	1.13	627	6			
32	13809	56.6	F	3.6	10 + 28	0.16	1.13	720	4			
33	16780	40.9	F	5.5	4 + 32	0.07	1.13	759	6			
34	10523	44.9	F	6.6	10 + 48	0.09	1.17	470	14			
35	16697	65.2	F	2.1	16	0.08	1.22	316	4			
36	4098	61.6	F	13.4	10 + 24	0.21	1.22	370	41	31	Abscess, right buttock.	Incision and drainage, right buttock.
37	16779	48.4	F	0.5	20	0.08	1.27	521	4			
38	16197	20.0	M	0.7	8 + 28	0.14	1.31	765	5			
39	16906	36.1	M	0.1	20	0.10	1.32	670	4			
40	16721	67.2	M	5.8	22	0.14	1.36	481	4			
41	16722	51.9	F	>0.1	20	0.13	1.36	647	3			
42	16729	58.1	M	0.4	32	0.08	1.39	571	8			
43	16341	65.6	F	17.9	34	0.19	1.41	271‡	5		Ulceration, great left toe.	None
44	8908	61.3	F	11.9	8 + 36	0.22	1.46	506	17		Ulcer, left foot.	None
45	4956	67.2	F	18.2	16	0.16	1.48	556	3			
46	12892	65.8	F	9.0	0	0.11	1.50	688	27	12	Gangrene, 3rd and 4th toes, left foot.	Left-thigh amputation.
47	1916	70+	F	24.0	4 + 22	0.14	1.64	538	7		Necrosis, left heel and left great toe.	None
48	5031	64.7	F	13.0	16	0.19	1.69	262	3			
49	15881	16.6	M	0.9	24 + 36	0.27	1.88	753	2			

*Bold-face figures represent protamine-zinc insulin.

†A second determination made 12 days later gave a fasting plasma value of 1.13 mg. per cent.

‡Collection incomplete.

of diabetic patients to the intravenous injection of a single large dose of ascorbic acid (1000 mg.).

SELECTION OF PATIENTS

Seventy-seven adult patients with proved diabetes were selected as subjects. There were 31 men and 46 women. The ages varied from fifteen to seventy-six, most patients being over fifty. In so far as possible, patients with diabetes under good control were chosen. The length of stay in the hospital prior to the test varied from one to one hundred and twenty days, in most cases three to eight days. Some patients were included who, although suffering from lesions of the extremities, or convalescing from operations for them, tioning, and in most cases it seemed reasonably adequate. This might be expected because in 36 of the 49 cases listed in Table 1 the duration of diabetes was of more than one year and in 33 of more than two years, and during this time almost all the patients had been following, more or less faithfully, diets which included vegetables and fruit in adequate amounts. The hospital diet averaged: carbohydrate 142 gm., protein 68 gm. and fat 85 gm. per day, and as the chief source of vitamin C it included two or three daily servings of raw fruit and vegetables. Some vitamin C may also be assumed to have been derived from the cooked part of the diet.[14] Calculated roughly, the daily average minimum intake of vitamin C on the

hospital diet may be taken as 80 to 140 mg., at least twice as much as the 40 to 60 mg. considered as the daily human requirement.[15, 16, 17]

METHODS

The method used for the determination of vitamin C was the 2, 6-dichlorophenolindophenol titration procedure of Tillmans.[2] For urine the Harris-Ray modification[18] was employed, and for blood the macro procedure as outlined by Farmer and Abt.[19] The indicator (La Motte) was dissolved in freshly boiled distilled water (85°C.), and was prepared so that 1 cc. was equivalent to about 0.05 mg. of ascorbic acid. The dye solution was standardized against known ascorbic acid (Merck's Cebione) and preserved in a glass-stoppered brown bottle in a refrigerator. Under these conditions it maintained its strength for two or three weeks.

Our procedure was as follows. A fasting blood sample was taken, and immediately afterward 1000 mg. of Vitamin C Injectable* was given intravenously. The urine voided during the following five hours, including that voided at the end of the period, was collected and kept in the refrigerator until just before titration. As preservative, sufficient glacial acetic acid was used to give the total sample a pH of between 3 and 4. Under these conditions we found no appreciable loss of ascorbic acid during the five-hour interval. At the end of the collection period the urine was measured and a convenient dilution (usually 1:100) was made for titration. Titration was carried out immediately and completed within one minute. There was seldom any difficulty in obtaining a sharp end-point in the diluted urine sample.

The blood plasma was precipitated as soon as possible, and the titration carried out, usually within one hour of collection.

For normal values in the saturation test we have used the figures suggested by Wright,[13] who states that normally 400 mg. or more of the total 1-gm. dose is excreted during the first five hours. For fasting blood values we have taken 0.80 mg. per cent as the lower limit of normal.

RESULTS

Table 1 shows the results obtained in 49 of the 77 diabetic cases and Table 2 those obtained in the 6 normal ones. Two points are evident. First, the vitamin C values obtained in the patients with uncomplicated diabetes were in general within a normal range and compared very favorably with those in the normal individuals, although on the average the latter were at a higher level. Secondly, the surgical cases tended to have either a lowered blood ascorbic acid or a diminished urinary excretion or both.

Of the total of 49 diabetic cases only 6 showed definitely low values in both blood and urine, not only with the blood ascorbic acid under 0.80 mg. per cent, but also with the urinary excretion during the five-hour period under 400 mg. Of these cases, 4 (Cases 1, 2, 9 and 13) were surgical. Therefore in only 2 of 49 cases of uncomplicated diabetes was there any striking indication of vitamin C deficiency.

That the fasting blood value usually bears a direct relation to the excretion is also evident from Table 1. In the cases in which a discrepancy may be noted, usually either the blood or urine value is a borderline figure or the patient falls in the surgical group. Thus, of 7 cases with blood values under 0.80 mg. but with urine excretion over 400 mg., 3 gave borderline figures with excretions under 410 mg. Two of these, and 1 other of the 7, were surgical patients. Similarly of the 8 cases with blood values above 0.80 mg. but with excretion under 400 mg., 5 were surgical cases and 4 had borderline blood values between 0.80 and 1.03 mg.

If we omit, therefore, all cases showing low values in which any surgical lesion might be a complicating factor, 9 diabetic patients out of a total of 49 cases gave some indication of a lowered vitamin C status: 2 (Cases 3 and 5) showed definite vitamin C deficiency, with blood ascorbic acid less than 0.80 mg. per cent and urine excretion for the five-hour period well under 400 mg.; 3 (Cases 16, 35 and 48) showed lessened excretion but normal blood values; and 4 (Cases 4, 5, 7 and 12) showed blood values under 0.80 mg. per cent but excretion above 400 mg. Of the remaining 40 cases, either both blood and urine values were above normal or a surgical complication could account for one or both lowered values. Only 1 patient (Case 46), with a lesion of the extremities serious enough to demand operation, had high values in both blood and urine.

The results obtained in the first 28 diabetic patients studied were discarded, and the data were not included because certain technical discrepancies were discovered which we felt invalidated the strict accuracy of the figures obtained. It is of interest to note, however, that in this group the general findings agree with those already stated. In most cases consistent values were obtained in the fasting blood sample and the five-hour excretion, and of those cases showing a low value for the five-hour period 58 per cent were surgical cases.

*Furnished through the courtesy of Hoffmann-LaRoche, Incorporated, Nutley, New Jersey.

DISCUSSION

The data presented above indicate clearly that in our series the average patient with uncomplicated diabetes can and does have a normal status as regards vitamin C. It must be remembered that our results were obtained with patients in a private hospital, and that findings in a large public clinic might be quite different. Our results are of significance, however, in ruling out any marked influence of the diabetes per se. The normal status of the patients observed in the present study no doubt reflects the adequate amounts of vitamin C afforded by the fruit and vegetables in their usual diet. With the increasing and laudable tendency to make diabetic diets more nearly like normal ones, this conclusion emphasizes anew the value of fruit, especially citrous fruit, and green vegetables, as included in the classic dietaries for patients with diabetes.

In our study, as previously stated, we have accepted Wright's values as a normal response to his saturation test. Ralli's recent work[20] with a series of 12 normal individuals, although she used smaller doses, tends to confirm the validity of Wright's results. Although the term "saturation" is somewhat vague and saturation tests are perhaps justly criticized as creating distinctly unphysiologic conditions, recent investigators seem to favor this method of determining the vitamin C status of an individual. The saturation test based on a single large dose of vitamin seemed more suited to our facilities than one involving a more prolonged period. The size of the dose obviated any slight effect of dietary variations during the test, and the analysis of urine high in vitamin content and preserved only five hours eliminated many technical difficulties inherent in the indophenol titration of urine.

Table 2. *Vitamin C Findings on Normal Individuals and Effect of Vitamin C on the Blood Sugar of Normal Fasting Individuals.*

Case No.	Vitamin C			Blood Sugar Content				
	Injected	Fasting plasma content	Urine excretion	Before injection	½ hr. after	1 hr. after	2 hr. after	4 hr. after
	mg.	mg. %	mg.	mg. %	mg. %	mg. %	mg. %	mg. %
1	1000	1.46	728					
2	"	1.69	612					
3	"	1.55	585					
4	"	1.22	495					
1	300	1.22		98	98	94	101	103
2	300	1.41		102	99	100	103	
5	1000	1.79	886	88	89	91	88	
6	1000	1.50	738	98	98	96	98	

Although the reliability of results obtained by the direct titration of urine with indophenol may be questioned owing to the presence of interfering substances, there is good evidence that after a large dose of vitamin C the reducing substance in the urine is chiefly ascorbic acid.[21, 22] The suggestion of van Eekelen and Heinemann[22, 23] that the urine of diabetic patients differs from normal urine in its larger content of non-specific reducing material, particularly thiosulfate, has not been apparent in our work. In view of the experiments of Heinemann,[24] no particular difference would be expected provided that there was no evidence of abnormal protein catabolism in the diabetic patient and that his protein intake corresponded closely to that of the normal controls.

As regards any difference between the normal and the diabetic individual in retention of ascorbic acid, our results, as evidenced in Tables 1 and 2, are in entire disagreement with those of Schroeder,[9] to whose work reference has been made. He asserts that after a given dose the diabetic patient retains a much greater proportion of ascorbic acid than does the normal individual and that with an intravenous injection of 150 mg. the retention may reach 97 per cent, even if the injection is repeated for several days; similarly 91 to 97 per cent was retained after the oral administration of 300 mg. These figures imply an excretion of only 3 to 9 per cent. From a study of the literature on urinary excretion and retention with which we are familiar, no explanation of such a low excretion seems probable except a diet definitely poor in vitamin C. It would be of interest to know the vitamin C content of the "usual diabetic diet" referred to by Schroeder, and also the blood ascorbic-acid levels of his patients.

It may be observed from Table 1 that several of our patients showed high fasting blood-sugar values. Ralli's[25] statement that the reabsorption of vitamin C and that of glucose do not involve a common mechanism justifies us in assuming that vitamin C absorption and excretion are independent of glucose absorption and excretion, and that high blood-sugar values probably do not influence vitamin C results.

Surprising to us were the low values obtained for both blood and urine ascorbic acid in surgical cases. These results were unexpected because, realizing the influence of infections on the vitamin C requirement, we carefully chose surgical patients long removed from active infection and from any surgical procedures. Our tests on this group were usually performed just prior to the patient's discharge, at a time when local lesions were uninfected and insignificant. The surgical patients were without exception those whose lesions were of the extremities. Because of the nature of the operations and of the anesthesia (usually low spinal), surgical procedures caused little or no interruption to the usual diet. It

seems likely that the generally lower economic status of the patients in the surgical group was partly responsible for the lower vitamin C values obtained.

In order to detect any possible hypoglycemic action of vitamin C, in a considerable number of cases the blood sugar was followed during the saturation test. Table 2 shows the results obtained with normal individuals in the fasting state. These persons obviously were in excellent vitamin C nutrition. It is clear that the injection of either 300 or 1000 mg. of ascorbic acid had no effect whatever on the blood sugar.

In the diabetic cases similarly studied the blood sugar was followed first on a control day, and then on the day on which the injection of 1000 mg. of vitamin C was made. Determinations were made before injection and at two-hour intervals afterward for a period of six hours. These patients and the 4 normal individuals likewise treated were not fasted, and the unavoidable variations in blood sugar, particularly in the diabetic cases, due to intake of food make the results difficult to interpret. The data, though not presented here, confirm, however, the completely negative findings secured with the fasted normal individuals. Our results suggest, therefore, that vitamin C has no significant effect on the blood sugar of individuals in good vitamin C nutrition. Whether the point of good vitamin C nutrition is a fundamental one we are not in a position to state, but the work of Sigal and King[26] suggests that possibility. They found a significant rise in fasting blood sugar and a distinctly lowered glucose tolerance in guinea pigs kept for ten to twenty days on a diet depleted in vitamin C but normal in other respects. A striking return to normal was found within fifteen days after vitamin C was restored. If a deficient diet incident to poor economic conditions causes in some large groups of diabetic patients a condition bordering on a state of subclinical scurvy, this work may offer an explanation of some of the conflicting reports in the literature.

SUMMARY

The vitamin C status of 77 adults with diabetes mellitus was determined. Results are reported in detail for 49 patients.

Patients with uncomplicated diabetes whose vitamin C intake had been adequate showed levels of blood ascorbic acid (fasting) above 0.80 mg. per cent, and excreted in five hours upward of 400 mg. of ascorbic acid in the urine in response to a 1000-mg. test dose given intravenously.

Patients confined to bed with surgical lesions, usually of the extremities, even with no fever or apparent infection, tended to show low normal or subnormal values. This may in part reflect a deficient vitamin C intake (prior to hospital admission) incident to an economic status lower than that of the majority of the patients studied.

With 4 normal individuals in good vitamin C nutrition no effect on the blood sugar could be observed after the intravenous injection of either 300 or 1000 mg. of ascorbic acid.

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CYSTOCELE REPAIR*

Factors Which Necessitate Changes in the Usual Procedure, With Suggested Technics

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THIS paper discusses some of the complicating situations which make it necessary to alter the usual methods employed in the repair of cystocele. Such repairs are usually a part of more general prolapse operations, and it is unavoidable that the larger problem of prolapse repair be also discussed here. In the last few years I have been surprised to note how frequently such complications are seen, and have observed that little help for the inexperienced operator is to be found in textbooks.

An almost infinite variety of situations may be present. Correct evaluation of the various factors involved and judicious variation of operative methods are necessary if a result satisfactory not only to the surgeon but to the patient is to be obtained. Only a few of the complicating situations will be discussed, and it is assumed that there has been a general acceptance of the thesis that hernias of the uterogenital hiatus are most advantageously repaired by the vaginal route. The general principles of such repair were admirably summarized two years ago by Ward[1] in an address before the British Congress of Obstetrics and Gynecology.

Suspension of the uterus or abdominal fixation has little place in this field, and such operations frequently interfere with an adequate vaginal repair if this is necessary at a later date. Several years ago I discussed before this society the case of such a patient, whose prolapse had been subjected on three previous occasions to abdominal suspension. At the last operation an actual fixation of the fundus to the abdominal wall was done; this fixation held the uterus but a large cystocele recurred. I was able to obtain a lasting satisfactory repair by cutting loose the fundus from its abdominal attachment, closing the abdomen and immediately performing a vaginal hysterectomy with the usual repair. Several other cases have been seen in which a well-sustained round-ligament suspension operation made subsequent repair of a cystocele quite difficult.

It is a sine qua non in plastic surgery that ideal conditions must obtain, especially as regards infection, before a successful operation can be contemplated. It is my belief that no cystocele or other major vaginal repair work should be done in the presence of a complete tear of the anal sphincter. Certainly this is true if such a tear allows incontinence of feces sufficient to alter the bacterial flora of the vagina. In such cases it is wiser to repair the anal sphincter first and complete other vaginal procedures at a later date. Fortunately this complication is seldom seen; for complete perineal tears are most likely to occur in the patient who has a funnel pelvis, the narrow pubic arch not only forming a secure attachment for the connective-tissue support anterior to the cervix but protecting this area from injury by the baby's head during delivery. I have, however, operated on 2 such patients by the two-stage procedure.

Where the cystocele presents the principal lesion from the points of view of both symptoms and deformity, I have found the interposition, or more properly the transposition, of the uterus a highly valuable and satisfactory method. The cervix is amputated whenever it is diseased, but this complicates the operative procedure, and in recent years I have been inclined to give up the interposition operation where the cervix had to be amputated and to perform the so-called Manchester type of operation instead. The interposition operation is further limited in its scope by the following considerations: the uterus must be approximately normal in size, cancer must be ruled out and further childbearing must be eliminated. If an enterocele is present its repair complicates the interposition operation and makes me favor the Manchester procedure or vaginal hysterectomy. I have also found the interposition operation a poor method where there is more than first-degree descent of the uterus. On the other hand, many patients having a cystocele with partial incontinence have been greatly benefited by the interposition operation, owing, no doubt, to the pressure of the transposed fundus against the symphysis. Whenever the intra-abdominal pressure is increased, this pressure of the uterine fundus is sufficient to compress the urethra and control the voluntary type of incontinence.

Poor results of prolapse repairs are frequently due to a failure to recognize and obliterate properly an enterocele or cul-de-sac hernia. I recently saw a patient of seventy-five with a pro-

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trusion of the cervix outside of the vulva. She had just been operated on suprapubically for relief of a large bladder stone. Ten years before this, one of my gynecological colleagues had repaired the cystocele but had failed to amputate quite enough of the cervix or to repair a deep enterocele. The cystocele repair was perfectly sustained, although the cervix was pulled too close to the symphysis. This undoubtedly accentuated the cul-de-sac hernia and placed the cervix far in front of the mid-axis of the pelvis in a position where prolapse was inevitable. I believe that the bladder stone, the result of chronic cystitis, was due to a sacculation of the bladder not in its usual cystocele area but on top of and behind the atrophied uterus. Pessaries are of no use in a case of this sort, and proper repair at the present time involves considerable risk. This case is discussed not only from the point of view of failure to repair the enterocele but to emphasize the necessity of locating the cervix in, or if possible behind, the mid-axis of the pelvis where some support may be obtained from the perineum.

That perineal support is not always effectual, however, is shown by the following experience. Six years ago I operated on a patient fifty years old to repair a large enterocele and rectocele, building up so high and firm a perineum that there was subsequently considerable complaint from dyspareunia. Two years ago the patient had an emergency laparotomy for gangrene of the omentum, and during convalescence considerable straining occurred due to vomiting. Almost immediately after convalescence she noted increasing symptoms from a cystocele which was not present at the time of my first operation. Repair of the cystocele and urethrocele was done although an extensive perineotomy was necessary. While no well-developed cystocele was present when I first saw this patient, I feel reasonably certain that there must have been some recognizable weakness of the pubocervical tissue. I do not advise routine repair of the anterior vaginal wall, but I do believe that even slight weaknesses of this tissue should be repaired, especially in women who may subsequently be called on to do heavy work. This is especially true where the operation is done before the menopause has set in, and where due regard must be given to the possibility of future hernia caused by the atrophic process of the menopause.

One year ago I was faced with a very unusual complication in a patient of only fair physical condition, aged seventy. She had a second-degree prolapse of the uterus with cystocele and rectocele and a true prolapse of the urethral mucosa. About half the urethral wall had everted, forming a mushroom-like tumor 3.5 cm. in diameter, portions of which were gangrenous. The patient was immediately sent to the hospital, and the prolapse of the urethra was reduced and corrected by the ingenious method devised by one of our members, Dr. Thomas N. Hepburn.[2, 3] This method consists, as is well known, of an extraperitoneal suprapubic incision, rapid blunt dissection of the space in front of the bladder and urethra, and suspension of the urethra and bladder neck to the posterior wall of the symphysis, the upper sutures fastening the wall of the bladder just above the bladder neck to the undersurface of the rectus fascia near its insertion in the symphysis. This patient voided voluntarily and made an uninterrupted recovery without permanent damage to the urethral mucosa. In order to prevent the cystocele and prolapse from dragging down the suspended urethra a Gellhorn pessary was worn for four months, and the prolapse was then repaired by the Le Fort method. Subsequent examination showed that the urethra had retained its high position, that there was no recurrence of prolapse, and that the patient was perfectly comfortable.

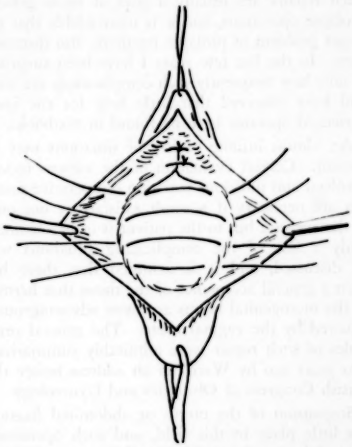

Figure 1. *A Commonly Employed Method of Reduplicating the Bladder Fascia.*

In the Manchester type of operation the lower sutures also grasp the anterior surface of the uterus. Inadequate attention to the bladder neck and middle urethral sphincter is illustrated.

Ordinarily the patient with a cystocele is interested in two things; the relief of protrusion, and

the relief of partial urinary incontinence or difficulty in emptying the bladder. Any of the usual methods will satisfactorily overcome the protrusion, but a complete restoration of normal urinary function is a more difficult affair. We distinguish two types of incontinence: that due to inadequacy of the involuntary bladder-neck sphincter, which occurs usually at night, and that which occurs on coughing and sneezing owing to inadequacy of the voluntary middle sphincter of the urethra. Kennedy[4, 5, 6] has shown that the middle sphincter is functionally and anatomically a portion of the levator musculature, and that this type of incontinence is due either to a stretching of this sphincter or distortion of the lumen of the urethra

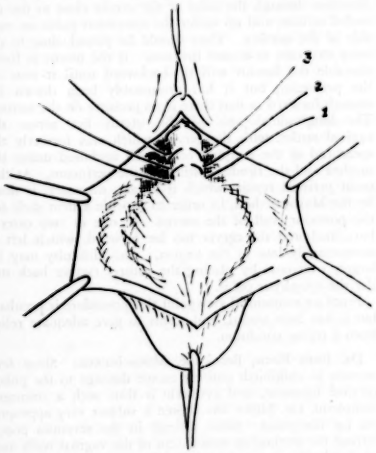

Figure 2. *Showing the Extensive Lateral Mobilization Necessary to Allow Adequate Repair of the Urethral Sphincters.*

Mattress sutures are placed so that the supporting sling of the middle sphincter is reconstructed; this elevates the urethra and bladder neck.

by scar-tissue contraction of lacerations of the sphincter. Satisfactory results can be obtained by freeing the entire posterior surface of the urethra and removing any distorting scar tissue, following this by reefing of the middle sphincter with mattress sutures, placed in the same manner as advocated by Kelly for incontinence at the bladder neck.

Kennedy's work has called attention to one of the principal sources of dissatisfaction in cystocele repair operations, and he emphasizes a point which many of us have already observed, namely that many women with a complete prolapse have no incontinence on straining until the floor of the bladder has been elevated by what seems to be an adequate pelvic repair. We are then surprised to find that incontinence on straining is almost a worse complaint than the previous prolapse. It is obvious that we must recognize the need for proper repair of the middle sphincter when we are repairing the bladder hernia.

Since following Kennedy's procedure I have had fewer failures in this regard. The operation is much more radical, and carries with it the necessity of catheter drainage for one or more weeks postoperatively. Employment of a retention catheter for at least five days is useful. Bladder irrigations are given from the first day until well after voluntary urination and complete emptying have been observed. It is useful to pass a urethral sound if the patient has been unable to void by the tenth day, in order to dilate the urethra, which may have been repaired too snugly. Giving bladder irrigations from the start has minimized the incidence of postoperative cystitis. During the last year I have been forced to perform this operation on several patients who had previously had what seemed to be an adequate cystocele repair.

One of the most interesting complications which we meet is the presence of a cystocele and a fair-sized uterine fibroid tumor in the same patient. When first seen, especially if the fibroid involves the cervix or the lower fundus, the cystocele may not be in evidence, and may not be noted until a later date if a supravaginal hysterectomy be done. If, however, a total hysterectomy is performed, one is able to observe the enormous dilation of the vagina and to note the presence of a cystocele. Following the work of others and inspired by watching Dr. Joe V. Meigs, I have with great satisfaction combined total hysterectomy with repair of the cystocele done by the abdominal route. This is made more difficult by extreme obesity, and necessitates the careful disinfection of the vagina before operation. I have found it to be a straightforward procedure which has given excellent postoperative results and which can be performed as quickly as if done from below. The repair of the perineum and rectocele can be done at the close of the operation if the patient's condition warrants. There is only one technical drawback to this procedure: it is not so easy to repair a urethrocele and an inadequate middle sphincter as it is by the vaginal method of Kennedy. In one case I tried with only partial success to do this by combining total hysterectomy and cystocele repair with a suspension of the urethra as proposed by Dr. Hepburn. The follow-up showed an entirely adequate result so far as the cystocele

was concerned, although there remained some rolling down of the suburethral structures. The urinary function, however, was quite normal, and a subsequent urethral repair of the Kennedy type may be done if necessary.

Serious physical debility caused by old age or by any major organic disease is not necessarily a bar to successful reconstructive pelvic surgery, although a proper choice of anesthesia and operative technics which cause little strain are necessary. In the feeblest patient one can afford marked relief by the Le Fort operation and I have been especially impressed with the modification of this technic suggested by Goodall and Power,[7] of Montreal. This modification lends itself most easily to include an adequate repair of the urethral sphincter and of the rectocele.

CONCLUSION

This paper has presented only a few of the many complicating situations met with in reconstructive vaginal repair work. In no branch of surgery do experience and ingenuity count so largely for success as in plastic work. We should study most carefully our failures, for, as Carlisle said, "It is more profitable to reckon our defects than to boast of our successes."

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Discussion

Dr. James B. Woodman, Franklin, New Hampshire: One thing in Dr. Miller's very interesting paper which impresses me is his assertion that no one type of operation for cystocele seems applicable to every case. That this must be so becomes evident when we consider that there are first, second and third degrees of prolapse, all accompanied by more or less stretching and dragging down of the bladder and rectum. There are also those cystoceles and rectoceles which have little if any prolapse.

The fact that we have run the gamut of operations, from the old Emmet butterfly procedure to the interposition operation and vaginal hysterectomy, and are still looking for a more satisfactory method, indicates that Utopia has not been reached, and that each case presents a problem in itself.

I have frequently seen cases of prolapse and cystocele in which operation has been followed by recurrence. In treating several of these I used a procedure described some years ago by the late Dr. H. L. Smith, of Nashua. This operation seems most applicable in the cases of old women where there is a marked postoperative cystocele, with a highly mobile uterus and some degree of secondary prolapse, and in which there is no connecting band between the fundus of the uterus and the abdominal wall. The cervix is grasped and drawn down. An elliptical plate of mucosa from the anterior vaginal wall is taken off down to the bladder musculature. The anterior edge of this section should be about 2 cm. behind the urinary meatus, and the denuded portion toward the cervix should include that structure, the cervical surface being denuded deeply and nearly to the margin of the cervical os. These two points are the most important ones of the procedure, and their observance will prevent later protrusion of the cervix.

The denuded elliptical area is closed with chromic catgut sutures in a transverse line up to the cervix on both sides. Two heavy sutures are passed in an anteroposterior direction through the sides of the cervix close to the denuded section, and up under the symphysis pubis on each side of the urethra. They should be passed close to the bony structure to ensure firmness. If the uterus is freely movable the fundus will tip backward until it rests on the perineum, but it has presumably been drawn far enough forward so that there is no pressure on the sacrum. The longitudinal axis of the uterus lies across the vaginal outlet, with the cervix, which was formerly the spearhead of the escaping cone, well anchored under the urethra and the fundus resting on the perineum. At this point perineal repair, which is usually necessary, is done by the Mayo method, in order to provide a firm shelf for the posterior wall of the uterus. In one or two cases I have anchored the cervix too far forward, which left it unnecessarily low in the vagina. This difficulty may be largely overcome by placing the sutures farther back under the symphysis pubis.

From an anatomical viewpoint this procedure is peculiar, but it has been useful, and seems to give adequate relief from a trying condition.

Dr. John Rock, Brookline, Massachusetts: Since few women in childbirth entirely escape damage to the pubocervical ligament, and cystocele is thus such a common complaint, Dr. Miller has chosen a subject very appropriate for discussion. Since Emmet in the seventies popularized the method of denudation of the vaginal walls and of the development of epithelial flaps, a great deal of water has passed under the arch; so that although the underlying principle of the repair of bladder hernia is still but the application of anatomical knowledge, one now expects the surgeon to understand the art of dissection and reconstruction, and especially, as Dr. Miller points out, to discriminate in the choice of which anatomic factors to utilize. He properly reminds us that suspension of the uterus will not by itself hold the bladder out of the vagina. When herniation of the bladder occurs it is not because its uterine attachment has descended, but because fascial support between the cervix and the symphysis has been weakened. For a permanent cure, reconstruction of this support is necessary.

Dr. Miller warns against repairing the anterior wall and a complete perineal tear at the same time. At the Free Hospital for Women it is customary to repair both simultaneously, since we have no appreciable trouble from breakdown of the anterior plastic, even when the posterior wound has suppurated. Dr. Frank A. Pemberton, following the late Dr. William P. Graves, emphasizes the importance of careful hemostasis, as well as the necessity in all plastic work, of tying all sutures without great tension;

for he believes that breakdown of a wound in the vagina is likely to result from retained blood clot and the cutting through of sutures.

The Watkins interposition operation has never been a favorite with us. We seem to obtain equally good results in the repair of large cystoceles associated with normal uteri, with or without elongated cervices, by advancement and reefing of the bladder, reconstruction of the pubocervical ligament and amputation of the cervix if necessary, without the gross interference with normal anatomy which the interposition operation entails. Like others, we have found that abdominal suspension of the uterus is unnecessary if such repair is accomplished below, unless there be prolapse or symptoms of retroversion. If the cystocele is accompanied by prolapse of the normal uterus, the latter is relieved by approximation of the cardinal ligaments in the midline, which shortens them and thus lifts the uterus — the so-called Fothergill or Manchester technic. Such a procedure is commonly expected to interfere with a subsequent delivery from below, so that in certain women it may properly be accompanied by ligation and transection of the tubes, a comparatively simple adjunctive procedure when done after advancement of the bladder and before reconstruction of the pubocervical ligament.

Dr. Miller emphasizes the importance of careful routine search for enterocele, which so often accompanies prolapse. If present the sac is developed and excised, the stump being attached to the posterior wall of the cervix, provided this has not been removed. If complete hysterectomy has been performed, the stump, together with the uterosacral ligaments, is attached to the base of the broad ligaments. For procidentia we do a vaginal hysterectomy or a Fothergill operation, or a colpocleisis, as seems indicated by the degree of prolapse, the condition of the uterus and the age and condition of the patient.

In all our cystocele operations, exposure and approximation of the subepithelial tissue is carried well forward and laterally to include the region under the neck of the bladder, in accordance with the teaching of Kelly, and later of Kennedy, that support here is essential for the relief of incontinence.

I have never excised redundant vaginal epithelium from above in the course of a complete hysterectomy. When hysterectomy is contemplated, vaginal examination under anesthesia is made, as it is before every abdominal operation, and we believe that the relaxation of the vagina and the cystocele can be diagnosed more accurately and be repaired more safely from below, before the abdomen is opened.

In agreeing as to the value of the Le Fort operation in elderly women, I should like to mention also the advantage of local anesthesia combined with morphine and scopolamine in suitable subjects. At the Free Hospital lately four operations in women over eighty and many others in slightly younger women have been easily and smoothly done, with no complications and with good results.

I am grateful for this opportunity to emphasize Dr. Miller's advice that varying anatomic and pathologic conditions necessitate various operative procedures, and that the surgeon when applying them must be ever aware both of the physiology of bladder control and of subsequent demands on the vagina.

Dr. Joe V. Meigs, Boston: Ten years ago I operated on a girl with a fibroid. As she had a moderate endocervicitis I cauterized the cervix; seven years later she came back with cancer of the cervix. Four years ago I operated on another woman with abnormal uterine bleeding, cauterized the cervix and removed the uterus supravaginally; three years later she developed cancer of the cervix. Both patients are dead, but both would be alive if total hysterectomies had been done. I have no faith in cauterization of the cervix as a prophylaxis against cancer. Since then I have leaned more toward total hysterectomy. I formerly endeavored to use Schiller's test and the colposcope to determine when the cervix was dangerous and when it was not, but without complete success. Now if I see what I think is a dangerous cervix, I remove it. If a patient with such a cervix needs abdominal surgery, I believe that a total hysterectomy should be done.

I have puzzled about the repair of a cystocele when doing a total hysterectomy. I had found that on dissecting the bladder free in front of the uterus I ran into the sutures I had used below in the repair of the cystocele, so I discarded that method. It is easy to remove a sufficient amount of anterior vaginal wall from inside to cure the cystocele; as the vagina is pushed off the bladder wall as large a piece as is needed can be removed. When the patient is turned around into lithotomy position it is obvious that the bladder is held sufficiently high and the cystocele has disappeared. Since first adopting this procedure I have operated on 50 or 60 cases in the same way.

If abdominal surgery is to be done, it should come first, as the major consideration: to repair a cystocele or perineum, or amputate or repair a cervix, with consequent loss of blood and consumption of time, followed by an abdominal operation, is an incorrect approach if it can be avoided. Vaginal examination and preparation should precede the abdominal operation, following which the patient is again placed in lithotomy position and the perineum is repaired. Occasionally a urethrocele is denuded and sutured.

In repairing urethroceles by the Kennedy method I have found fine silk sutures a great help; the knots are very small and more sutures can be taken. I have done about 15 repairs in this way, and in no case has a wound broken down or have sutures had to be removed.

Dr. Thomas N. Hepburn, Hartford, Connecticut: Dr. Miller has asked me to speak of the technic of the operation which he has used for urethral prolapse. This type of urethral prolapse is more than what Dr. Miller referred to as a "mucosal prolapse." It involves the whole urethral wall. When I first saw this condition eighteen years ago in a child five years old, I was at a loss as to how to treat it, because all the literature at that time referred to circumcision as the only possible treatment. The prolapse impressed me, however, as a true sliding hernia, requiring treatment as such.

A suprapubic, prevesical, extraperitoneal incision is made, following which the bladder neck falls away under the exploring finger. It requires no pressure to run the hand down under the symphysis and around the urethra. With the child's legs separated and an assistant looking at the urethra, traction is made on the bladder. The prolapsed urethra is easily pulled back with the bladder traction until the assistant announces that the hernia has disappeared; the bladder is then sutured to the periosteum behind the symphysis. This holds it in perfect position.

I am very thankful to Dr. Miller for having adopted this operation. I have had occasion to do it only four times, and I am sure that if any of you are confronted with the problem of urethral prolapse you will find this a very simple and satisfactory procedure.

Dr. Oliver N. Eastman, Burlington, Vermont: There are so many advantages in removing the uterus vaginally

instead of by the abdominal route that I advocate this operation whenever conditions warrant. I wish to describe briefly a procedure which has served me well in the repair of cystocele. I am able to report 300 cases in which I have employed it, and the results have been highly satisfactory.

After the uterus has been removed from below, the lateral uterine supports are approximated in the midline below the closed peritoneal cavity. The redundant mucous membrane is removed from the anterior vaginal wall, well up to the base of the urethra. Two sutures of No. 2 chromic catgut, one below the other, are utilized to close the bladder hernia. They pass through the mucosa, catching the pubic fascia, and laterally through the vesicocervical fascia to the anterior portion of the body formed by the union of the lateral uterine supports, catching the vesicocervical fascia on the opposite side and then the mucous membrane opposite the entrance of the suture. If a cul-de-sac hernia is present, similar sutures of a purse-string nature pass through mucosa and into the posterior portion of the central body. Lateral sutures pass through the mesial portion of the body and out on the opposite side. These sutures, designated as tension sutures, are allowed to remain lax until the vaginal mucosa and deeper structures are approximated by interrupted sutures. The tension sutures are then drawn moderately snugly, causing the vault of the vagina to assume a high position and effectually closing the space anteriorly and posteriorly to the central body.

In 18 cases in my series the patients were over seventy years of age and the operation was performed with local anesthesia, the tissues being infiltrated with 1 per cent novocain. Senility does not seem to be a deterrent factor, as the results are as good as in younger individuals. As a rule, also, the operation is more easily done because the tissues are less vascular. A retention catheter affords relief from bladder distention and obviates frequent catheterization.

A checkup on most of these cases has shown highly satisfactory postoperative results.

DR. CHARLES LARKIN, Waterbury, Connecticut: Dr. Miller said that in some cases of procidentia it is impossible to perform an interposition operation on account of the large size of the uterus. I venture to suggest that these large uteri may be shrunk to normal size by cauterizing the nabothian cysts or the erosions or eversions of the cervical lips which are so often present; or one may use the method advocated by Dr. John Fallon, of Worcester, to shrink the uterus by inserting well-screened radium into the uterine cavity. In about six weeks the uterus shrinks enough to permit this operation.

DR. MILLER (closing): I am not familiar with Dr. Smith's operation, reported by Dr. Woodman, but it recalls a similar one which I recollect as coming from Texas. With regard to not combining the repair of a complete tear with that of a cystocele, I believe that the men at the Free Hospital for Women probably take scrupulous care to obtain a normal flora in the vagina, which after all is the essential thing. The interposition operation is possibly finding less and less place. I certainly have found it so, but there are some occasions where with moderate incontinence it is a quick way out of the difficulty.

Dr. Meigs emphasized the importance of doing the abdominal surgery first. That certainly is one of the most important things brought out by this discussion. My paper did not concern itself with the ordinary type of cystocele and prolapse, but dwelt on some of the abnormal features which make us alter our technic; the need for doing the abdominal surgery first is one of these.

I should like to emphasize what Dr. Hepburn pointed out — that the dissection behind the symphysis is extremely easy. In this type of operation it is surprising to find that there is absolutely no supporting connection between the urethra and the symphysis. The bladder neck falls away as soon as the superficial tissues are separated.

REPORT ON MEDICAL PROGRESS

THE FAT-SOLUBLE VITAMINS*

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THE object of this article is to summarize contemporary knowledge of the fat-soluble vitamins, emphasizing particularly the facts of most interest to practicing physicians. To achieve this in a short space, it has been necessary to eliminate historical and bibliographical details, and to curtail discussion of controversial questions. For more complete treatment the reader is referred to the papers and reviews listed at the end of this article, and particularly to the series of articles which have appeared in the *Journal of the American Medical Association* during 1938. A similar article, dealing with the water-soluble vitamins, will appear subsequently.

VITAMIN A

Chemistry. Vitamin A has been isolated in chemically pure state, and its successful synthesis has been reported recently.[1] It is an unsaturated alcohol with the formula $C_{20}H_{29}OH$, and is a colorless compound chemically related to the carotenoids, a class of pigments widely distributed in plant tissues. Four of these pigments can be converted by the animal body into vitamin A, and are therefore called provitamins. The commonest and most important of these provitamins is β carotene.

Physiology. Vitamin A is absorbed in the intestine, passes into the blood stream via the thoracic duct and is stored in the liver. Carotene probably requires the presence of bile salts and fatty acids for its absorption. It passes directly into the blood stream and is taken up by the liver, where it is converted into vitamin A. Vitamin A is an essential constituent of visual purple (rhodopsin), a pigment found in the rods of the retina. Visual purple is necessary for the normal function of the rods in the appreciation of dim light.[2] Nothing is known of the biochemical action of vitamin A in other tissues.

Pathology. Vitamin A deficiency in laboratory animals is characterized by a morphologic disturbance of epithelial surfaces. The primary change is atrophy of the epithelium, followed by proliferation of the basal cells, resulting in the replacement of normal epithelium by a stratified keratinized layer resembling epidermis.[3] In the bronchial tree this lesion may block the small bronchi with epithelial plugs and give rise to localized bronchiectasis, atelectasis and, frequently, patchy pneumonia. In the cornea of the eye, xerophthalmia results, though generally late in the course of the deficiency. Similar changes can occur in the ducts of glands and in the urinary and genital organs. In the pelvis of the kidney this may predispose to the development of renal calculi, which sometimes occur in animals deficient in vitamin A. There is no general agreement however that calculus formation is a specific effect of vitamin A deficiency.[4] The normal development of teeth is also impaired by vitamin A deficiency.[5] While it has been reported that demyelination of the spinal cord and peripheral nerves can occur in deficient animals,[6] not all workers have found such lesions.[7] Growth is restricted in young animals suffering from vitamin A deficiency, but this is no more a specific effect than the lack of growth that occurs in deficiency of many other essential dietary constituents — other vitamins, essential amino acids and mineral salts.

Epithelial metaplasia similar to that found in animals may occur in man as a result of vitamin A deficiency. Xerophthalmia, though rare and a sign of severe deficiency, has been reported in this country.[8] Children with xerophthalmia succumb very easily to respiratory infections.[9] Skin changes, characterized by hyperkeratosis and absence of sweating, sometimes occur.[10]

Probably the most important effect of mild vitamin A deficiency is night blindness (hemeralopia). Subnormal dark adaptation can be detected with a photometer, and frequently occurs in apparently healthy people.[11] While there are certain difficulties in accepting photometer readings as a definite criterion of vitamin A nutrition,[12] there is no doubt that vitamin A therapy may result in striking improvement of subnormal dark adaptation. The importance of nutritional hemeralopia in automobile drivers has been stressed recently.[13] "Glare-blindness" (nyctalopia), occurring after exposure to bright headlights, may also be due to vitamin A deficiency.

Assay and Units. The vitamin A content of biologic substances is estimated by feeding tests on growing rats, by a color reaction with antimony trichloride or by spectrometry.[14] The last is prob-

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ably the most accurate method. Feeding tests measure the total vitamin A activity (both vitamin and provitamin). The other methods measure only the vitamin, although the spectrometric method can be utilized to estimate carotenoids separately. Depending on which method is employed, different units are currently in use to express the vitamin A potency of foods. The Sherman and international (U.S.P.) units* are used when the assay has been done by rat feeding tests. Lovibond blue units are used as a standard in the antimony trichloride color reaction; and the readings obtained by spectrometry are converted to international units by the use of a factor. This confusion is made worse by the fact that there is at present no general agreement on how many units of one standard correspond to one unit of another. Probably the best figures at the present time are as follows:[14, 15] 1 Sherman unit is equivalent to 1.4 international units; 1 blue unit is equivalent to 20 to 30 international units; and the factor most generally used to convert spectrometric readings into international units is 1/1600.

Sources of Vitamin A and Carotenoids. The most important sources of vitamin A in the human diet are milk, butter, eggs and liver. Carotenoids occur in association with chlorophyll and are therefore present in green vegetables, but not in the pale lettuce leaves which make up the ordinary salad. Carrots and sweet potatoes are good sources of carotenoids and derive their color from them. While color is an index of the provitamin content of milk and eggs, it is not a measure of the amount of the colorless vitamin present in these foods. Canning and cooking do not seem to alter the vitamin A activity of foods.

When it is necessary to supplement the diet with some more potent preparations, fish-liver oils should be used. Cod-liver oil is the most familiar preparation. The U.S.P. dose for infants is 1 teaspoonful (4 cc.), and for adults 2 teaspoonfuls (8 cc.) daily. The latter amount contains from 5000 to 10,000 I.U. (international units). Halibut-liver oil has usually from fifty to one hundred times the potency of cod-liver oil. The recognized dose (N.N.R.) for infants is 6 to 10 drops (0.15 to 0.25 cc.) daily. A suitable dose for adults is 10 to 20 drops (0.25 to 0.50 cc.) daily; it has the advantage that it can be taken easily by patients who find cod-liver oil unpalatable. In most cases, cod-liver oil is preferable, since cases of vitamin A deficiency may also be deficient in vitamin D, and cod-liver oil contains more vitamin D per dose than does halibut-liver oil. Furthermore the additional animal fat has nutritive value. In cases of severe deficiency, amounts considerably larger than the official dose may be given with safety.

Human Requirements. The probable minimum requirement of an average man is about 2000 I.U. a day, but due to variation in human weight and activity and in the vitamin content of foods, it is suggested that 3000 I.U. daily provides a safer margin in calculating dietary allowances.[16] This amount is obtained by the daily consumption of two glasses (500 cc.) of milk, one egg, three pats of butter (30 gm.) and a moderate helping of green vegetables.[17] Children probably require at least as much as adults. Infants will receive sufficient vitamin A if they are given cod-liver oil in the amounts recommended in the subsequent section on vitamin D.

Therapeutic Uses. Vitamin A therapy is essential in cases of severe deficiency with xerophthalmia and skin lesions. Patients who complain of night blindness or in whom photometer tests show an abnormal dark adaptation should receive a diet rich in vitamin A, and if necessary additional supplements of the vitamin in the form of cod-liver or halibut-liver oil. In cases of infection, particularly of the respiratory tract, attention should be paid to the dietary history, and if this seems to indicate that the vitamin A intake has been low, additional vitamin should be given. It is a commonplace that ill-nourished individuals withstand infection poorly, and though it is by no means certain to what extent vitamin A deficiency usually contributes to this lowered immunity, its possible influence should not be overlooked. In pregnancy, additional vitamin A may be beneficial. A quart of milk a day supplemented by two teaspoonfuls (8 cc.) cod-liver oil may be recommended as an addition to the usual diet. There is some evidence that additional vitamin A during pregnancy may reduce the incidence of puerperal infection,[18] although other more important factors are probably concerned. In addition it may possibly ensure that the colostrum and first milk is well supplied with the vitamin; this may be important in view of the fact that the livers of newborn babies contain very little vitamin A. Care should be taken to provide for an adequate vitamin A consumption in patients with a limited food intake from whatever cause. Vitamin A absorption is probably impaired in steatorrhea, and in liver diseases the storage of vitamin A may be disturbed; such cases possibly benefit by receiving additional amounts of the vitamin.

There is no good evidence that an excess of vitamin A in the diet of an individual already well supplied will lead to any increased immunity to infection. Its use as a prophylactic against colds

*One international or U.S.P. unit is defined as having the biologic activity of 0.6 micrograms of pure β carotene.

and influenza has no justification if the diet is adequate. It is doubtful whether vitamin A supplements have any beneficial effect in thyrotoxicosis, demyelination of the spinal cord, sexual disturbances or anemia.[4] It is probably ineffective in the treatment of urinary calculi[18] and in the local treatment of skin lesions.[4]

VITAMIN D

Chemistry. Vitamin D is not a single chemical entity; there are a number of known compounds which show vitamin D activity.[20] They are all sterols or steroids, and therefore chemically related to cholesterol and the sex hormones. Probably only two have practical importance. These are calciferol (vitamin D_2) and vitamin D_3.* These substances are formed from inactive provitamins by the action of ultraviolet light. The provitamin of calciferol is ergosterol, a substance found in yeast and fungi, but not in ordinary human diets. The provitamin of vitamin D_3 is 7-dehydrocholesterol, which is present in animal fats, liver, milk and butter. The conversion of provitamin to vitamin can take place in the human body if the skin is exposed to sunlight or to rays from an ultraviolet lamp.

Physiology and Pathology. Vitamin D controls the retention of calcium and phosphorus in the body. Deficiency of the vitamin increases the amount of calcium and phosphorus lost in the feces, and may decrease the concentration of these elements in the blood. In infants the following pathologic changes result: the deposition of calcium salts at the growing points of the long bones is delayed, and the amount of cartilage and osteoid tissue between epiphysis and diaphysis increases; the bones are deficient in calcium salts; and the development of teeth is impaired.[21] The changes are responsible for the characteristic deformities of rickets. Another feature of rickets is hypotonia, which may be manifested clinically by a protuberant abdomen and a delay in learning to walk. The level of phosphorus in the blood serum is usually reduced in active rickets — from the normal level of about 5 mg. per 100 cc. to 3.5 mg. or less. The serum calcium may also be reduced below the normal level (10 mg. per 100 cc.), and in such cases tetany is frequent. In adult women vitamin D deficiency may result in osteomalacia,[22] particularly at the time of pregnancy.

Other factors besides the dietary intake of vitamin D may influence the retention of calcium and phosphorus.[21] Not only must the diet contain adequate amounts of these elements, but there should be a proper balance between the amounts of each ingested. This may become important if the diet is restricted to certain foods and does not include milk. (Milk is a good source of calcium and phosphate in balanced amounts.) It is also important that the phosphates in the diet should be in a form that is readily absorbed, which is probably not the case when cereals are the main source of phosphates.[23] An acid-ash diet — rich in meat and cereals, poor in fruit and vegetables — may increase the loss of calcium in the urine. Finally the absence of sunlight prevents the activation of provitamin in the body and increases the need for active vitamin D in the diet.

Sources. It is a remarkable fact that most articles of human diet are poor in active vitamin D. The best sources are milk, butter, liver and eggs. A pint of summer milk ordinarily contains about 10 units,* a pat of butter (10 gm.) about 8 units, and one egg 20 to 60 units.[24] For therapeutic purposes very much richer sources of the vitamin are required. A great number of preparations containing concentrated vitamin D are now obtainable. Only the better known preparations will be mentioned here, but others may be used in appropriate doses. Cod-liver oil usually contains about 400 units per teaspoonful. It has the following advantages: it is cheap and safe, its fat content has nutritive value, and it may be more effective unit for unit than viosterol. Disadvantages are its fishy taste and the danger of lipoid pneumonia if it is vomited and inhaled. If cod-liver oil is not tolerated by the patient a more concentrated preparation may be used, such as tuna oil or viosterol in oil (preferably in oil which also contains vitamin A). Viosterol is obtained by ultraviolet irradiation of ergosterol derived from yeast. It is sold in concentrated oily solution, of which one drop contains 166 units.

Another way of giving additional vitamin D is in vitamin D milk. Three kinds are obtainable. Irradiated milk is standardized to contain 135 units per quart. Metabolized milk (obtained from cows fed with irradiated yeast) and fortified milk (milk to which vitamin D has been added) both contain 400 units per quart.

Requirements. The amount of vitamin D required by infants is probably variable, but in general it can be said that about 400 units a day are necessary to ensure against the onset of rickets and to promote optimum skeletal growth and dentition.[25] It is clearly impossible for an infant to obtain this amount from milk alone, and for this

*Since calciferol, vitamin D_3 and other known members of the vitamin D group have apparently identical biologic properties, it is possible for practical purposes to consider vitamin D as a single entity.

*Vitamin D activity is measured in international (U.S.P.) units. One unit corresponds to the activity of 0.025 micrograms of pure crystalline vitamin D.

reason all infants should be provided with some additional source of the vitamin. There are many different ways of making this provision. One procedure is to start in the first few weeks of life with ½ teaspoonful (2 cc.) of cod-liver oil (200 units of vitamin D) daily, and to increase this after some days to 1 or even 2 teaspoonfuls (4 or 8 cc., 400 or 800 units) a day. This daily dose should be maintained for the first two years at least, and preferably longer.[24] The need for the vitamin may be less in summer, but it is unwise to break the habit of taking the oil regularly when once it is well established. Premature infants require more vitamin D than full-term infants and should receive at least 800 units a day, preferably in some more concentrated preparation than cod-liver oil.

Little is known about the vitamin D requirements in childhood and adolescence, but a teaspoonful of cod-liver oil a day might reduce the incidence of dental caries, and promote optimum growth in children who are rarely exposed to the sun or whose diet lacks abundance of milk and butter.

Nothing is known about the vitamin D requirements of adults. It has been suggested that additional vitamin may be beneficial in the following types of cases: people kept from the sunlight for long periods, particularly bed-ridden invalids in whom the bones are becoming rarefied; patients recovering from fractures; and individuals with a poor dietary history, particularly if no milk — the main dietary source of calcium — has been taken.[24] Pregnant women should receive at least 800 units a day throughout pregnancy, together with a liberal supply of milk.

Therapy. In the treatment of rickets a good procedure is to start with three teaspoonfuls (12 cc.) of cod-liver oil (1200 units of vitamin D) daily, and to increase the dose if no improvement is evident after one month.[24] X-rays are useful in demonstrating the effect of treatment on bone formation at the growing points. Refractory cases of rickets that require relatively enormous doses[26] are occasionally encountered. In treating such cases care must be taken to avoid overdosage, which results in gastrointestinal symptoms and supranormal levels of calcium in the blood. Metastatic calcification may occur in the arteries and elsewhere, with serious consequences.

Vitamin D therapy has been recommended in a variety of conditions apparently unrelated to vitamin D deficiency. More work appears to be needed before these recommendations can be generally accepted.

Finally it should be emphasized that an adequate intake of vitamin D is not alone sufficient to ensure normal retention of calcium and phosphorus. The diet must also contain an adequate supply of these elements, and this is most easily provided by the regular consumption of milk or cheese.

VITAMIN E

The vitamin E activity of biologic materials is due to a group of chemical substances known as tocopherols. They are found in vegetable oils, particularly in wheat-germ oil. Vitamin E deficiency in rats results in sterility in the male, and resorption of the fetus in the female.[27] Nothing is known about the human requirements for vitamin E. There have been some reports suggesting that wheat-germ oil may be useful in the treatment of habitual abortion.[28]

VITAMIN K

Vitamin K is a fat-soluble substance found in a variety of foods. The best-known sources are alfalfa and decayed fish meal. Fowls deficient in this vitamin develop hemorrhages, which are probably due to a lack of prothrombin in the blood. Human cases of obstructive jaundice with a bleeding tendency may show an abnormally long prothrombin clotting time.[29] It has been recently suggested that this is due to failure to absorb vitamin K, in the absence of bile secretion. This hypothesis is supported by the observation that vitamin K taken with bile salts by mouth may improve the prothrombin clotting time in some cases of obstructive jaundice[30] and that vitamin K has been found to have the same effect in a few cases when given by intramuscular injection.[31]

CONCLUSIONS

An ample diet, well supplied with dairy products, provides sufficient fat-soluble vitamins for the needs of the normal individual, except during infancy, pregnancy and lactation. Deficiency of fat-soluble vitamins is liable to arise when the diet is restricted, particularly in infants and children who do not receive enough milk. Fish-liver oils correct such deficiencies but do not compensate for the lack of other essential dietary constituents supplied by milk.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 25021

PRESENTATION OF CASE

A seventy-seven-year-old, white, married man entered complaining of paroxysmal dyspnea, disorientation and generalized fibrillary muscle twitchings of four days' duration.

Approximately five years before entry the patient was admitted for a right inguinal hernia, constipation and a trace of glycosuria found in only one specimen. He drank rather large amounts of water and had nocturia several times each night. Walking caused his legs to ache. The previous year he had had sudden pain and swelling in the left foot. It remained colder than the other, with occasional slight swelling. His arteries were palpable and tortuous, his extremities cold and cyanotic. Examination of the heart at that time showed a rate of 48, with frequent dropped beats. There seemed to be slight enlargement to the left. No murmurs were heard. A_2 was louder than P_2. The heart sounds were of good quality. The blood pressure was 130 systolic, 80 diastolic. The lungs were clear. Simple therapeutic measures gave marked relief of most of his symptoms, and he was discharged.

Six weeks before entry he had had an attack of precordial pain and accompanying symptoms which his physician thought were due to coronary occlusion, but a series of electrocardiograms did not substantiate such a diagnosis. It was therefore decided that there was coronary sclerosis, probably without definite occlusion. Pulmonary rales appeared shortly thereafter, and there was questionable ankle edema. Digitalization gave relief, and there was definite improvement although the patient failed to regain his previous state of health. About four days before entry he developed Cheyne-Stokes type of respiration, apparent air hunger with paroxysmal dyspnea, disorientation and generalized muscle twitchings. He had lost 25 pounds in weight during the past year. There were occasional twinges of precordial pain. Extrasystoles had been noted from time to time.

Physical examination on entry showed a disoriented, moderately ill man with Cheyne-Stokes breathing. The skin and mucous membranes were dry but not discolored. The pupils were equal but reacted sluggishly to light. There was 3 to 4 cm. of dullness at the right base, and diminished breath sounds. Crackling rales were heard over both right and left lower lung fields. The heart rate was 100 and regular except for ventricular premature beats. There was a suggestion of early gallop, the sounds being of poor quality. No murmurs were heard. P_2 was greater than A_2. The left border was 12 cm. to the left of the midline. The blood pressure was 130 systolic, 100 diastolic. Examination of the abdomen was negative except for an easily reducible right inguinal hernia. Knee jerks and ankle jerks could not be obtained. There was no clonus. Babinski signs were equivocal. Numerous muscular twitchings were noted over the entire body, but no weakness or sensory impairment was elicited.

The temperature was 96.8°F., the pulse 100, the respirations 40.

Examination of the urine showed a specific gravity of 1.033, a slight trace of albumin, a rare red cell and 8 white cells per high-power field, no sugar and no diacetic acid. The blood showed a red-cell count of 4,640,000, 80 per cent hemoglobin, and a white-cell count of 13,200 with 86 per cent polymorphonuclears. The nonprotein nitrogen of the blood serum was 39 mg. per cent.

An x-ray film of the chest showed soft mottled dullness throughout the lower third of each lung field. On the left the shadow was most dense near the hilus, on the right at the extreme base. The heart shadow was indistinctly seen through the dull area and appeared to be only slightly enlarged. The apices were clear.

An electrocardiogram showed that T_1 and T_2 had become low compared with the record taken six weeks before entry. T_4 had changed in contour. The changes were in the direction of normal, although the T waves remained abnormal. The P-R interval was 0.18 second. The ventricular rate was 100, the auricular rate 100.

On the day after admission the patient's condition was worse. There was slight cyanosis of the lips and nails. The pulse rate was 110 to 120. Respirations were of a more accentuated Cheyne-Stokes character. However, he seemed less irrational. On the third hospital day neurological examination showed a suggestion of spasticity in the left leg, with occasional doubtfully positive Babinski and Chaddock signs. There was left facial weakness, and slight drooping of the left eye. The patient was incontinent. He muttered half-formed words and did not recognize the examiner. The following day he was still delirious but complained of an intermittent mildly irri-

tating discomfort in the left anterior chest, which was aggravated by breathing. He had an abortive coughing grunt in paroxysms at long intervals, but no expectoration. Physical examination was unchanged except that the left facial weakness was more marked, the leg signs had disappeared and the patient was rational for a few minutes.

On the fifth day he was up in a wheel chair. In the late afternoon he had occasional chilly sensations lasting about twenty minutes, followed by profuse sweating, but his temperature remained at 98°F. His pulse was 120, the blood pressure 100 systolic, 65 diastolic. On the sixth day the facial paresis had disappeared. His general motility had improved bilaterally, but there seemed to be less motion on the left. There was otherwise no change. On the ninth hospital day he was still confused. He had some difficulty in swallowing orange juice. Twitchings were still noted in the face, tongue and extremities. The heart was regular, with a rate of 108, gallop rhythm and sounds of poor quality. Rales remained at both bases. The left face was slightly weaker than the right. On the eleventh day rales were heard in the left back and axilla, with a few at the right base. The serum nonprotein nitrogen was 31 mg. per cent, the red-blood-cell count 4,800,000, the white-blood-cell count 14,100, and the temperature 96°F. On the fourteenth day he was sitting in a chair without apparent shortness of breath and without Cheyne-Stokes respiration. He had received aminophyllin for four days, and his output of urine had increased. An electrocardiogram showed lower T waves than in the previous records, apparently indicating increased myocardial damage.

There was marked Cheyne-Stokes breathing on the seventeenth day. The pulse was 130 to 140. A chest plate still showed mottled dullness in both lower lung fields, with no appreciable change since the last film. On the twentieth day there was slight edema of the back, and many rales in the left back and axilla. His condition seemed somewhat worse. The heart sounds were faint at a rate of 96 but fairly regular. His blood pressure could not be determined accurately; the systolic pressure was 95 to 100, the diastolic indefinite. The following day he showed a leaden pallor and was obviously running a downhill course. His urine output was decreasing, and edema increasing. The serum nonprotein-nitrogen was 109 mg. per cent. He continued to complain of pain in the left chest and could not lie on that side. The left arm was more swollen than the right. He became gradually weaker but passed a peaceful night. The following morning he gave a single gasp and died.

Differential Diagnosis

Dr. Howard B. Sprague: At first this case seems fairly straightforward, but there are a few factors that do not seem to fit into the diagnosis suggested by the history. His first admission can be summarized by saying that at the age of seventy-two he was examined and showed evidence of general arteriosclerosis, perhaps with a mild sclerotic diabetes. He had a history suggesting an occlusive episode in an artery of the foot. When they say his heart had a rate of 48 with frequent dropped beats, I suppose they refer to what was felt at the wrist rather than at the apex of the heart. He probably had premature beats that did not reach the wrist rather than heart block, because five years later, at the age of seventy-seven, he did not show heart block. His heart otherwise did not seem to be particularly involved, being only slightly enlarged, and he had a normal blood pressure, no heart murmurs and a good quality of heart sounds. Then we know nothing about him until six weeks before he entered the hospital, when he had an attack of precordial pain, from which he apparently never recovered to any appreciable extent, and developed a picture of congestive heart failure.

Precordial pain is not the type of pain that is ordinarily described in coronary occlusion although I have seen it with a proved diagnosis of occlusion. If he did not have a coronary attack at that time we have to think of pain of pericardial disease or pleural disease or some other pulmonary or mediastinal pain. We have no pleural or pericardial rub described. There is nothing to suggest that he had a dissecting aneurysm, either on physical examination or by x-ray, and in the absence of hypertension, that would seem to be unlikely. The findings then are congestive failure, with the congestion localized in the bases of his lungs.

Paroxysmal dyspnea and Cheyne-Stokes breathing are commonly seen in arteriosclerotic individuals with cardiac failure. He had lost 25 pounds in weight. Can we ascribe that to the arteriosclerosis, which often does result in loss of weight, or should we think of cancer? The heart examination on his second visit showed an increase in size; murmurs were still absent but there was a change in the heart sounds as they were of poor quality and there was a suggestion of gallop rhythm. The blood pressure had not been disturbed unless he had had some hypertension in the interim. The neurologic signs and generalized muscular twitchings do not mean very much to me. At his age, I

believe that very ill individuals can have general fibrillary twitchings over the entire body without its meaning a primary neuromuscular condition. His urinary examination at that time does not suggest that he had much impairment of function on a primary nephritic basis but a certain amount secondary to congestive heart failure.

DR. AUBREY O. HAMPTON: I am going to add the postmortem films in this case because they are of better quality. The first portable examination of the chest showed a relatively dense left midlung field and an obscured left side of the diaphragm, with a clear space between the lower and middle shadows. On the right side a rather dense shadow which runs irregularly downward along the heart shadow is seen, and this is fairly sharp in lateral outline. You do not see the diaphragm on either side. The heart is moderately enlarged in spite of the fact that this is a portable film. At the second examination the pulmonary conus, if that is it, is prominent, but the density in the lungs has changed very little. In the postmortem films the chest appears much clearer than in the antemortem ones. The disease that we might have suspected in the upper lobes is not certain, and all we see is homogeneous density at the right base and an indefinite, ill-defined, rather oval shadow on the left side, which is flat against the posterior chest wall at about the sixth rib. It looks quite a bit like encapsulated fluid, or even tumor can have this appearance. It is very sharp in outline in the lateral view, and it suggests an infarct because of this. The shadow here in the lateral view is along the superior margin of the lower lobe, and you cannot tell from this other view which lobe it is in.

DR. SPRAGUE: It looks from the x-ray films as if this man had died cured. To proceed: he ran a downhill course with some changes in the electrocardiogram which were not specific and with neurological signs which were variable and seemed to indicate minor occlusive episodes in the cerebral circulation. The cardiac findings on physical examination were those of falling blood pressure, the poor quality of the heart sounds increasing and gallop rhythm persisting. At the end his nonprotein nitrogen was increased to 109 mg. per cent, which I believe could be accounted for on the basis of congestive failure. He died rather suddenly.

The joker in the situation seems to be the pulmonary lesion. We must admit, I think, a generalized arteriosclerosis, and with changes in the T waves in the electrocardiogram, we cannot disregard the probability of coronary disease, perhaps of multiple coronary occlusion or a generalized process, without evidence of an acute large infarct. Are the changes in the lungs those of congestive heart failure which has been relieved, or are they those of multiple pulmonary infarction or cancer? The lack of progression of this picture is not in favor of cancer but of something which was remediable, and the best guess to my mind is pulmonary infarction, perhaps with some pleuritic response and accumulation of fluid. If these are pulmonary infarcts, it is not necessary to assume that they came from the heart because they may have come from the peripheral venous circulation. My diagnosis is generalized arteriosclerosis including cerebral and coronary sclerosis, with multiple small cardiac infarcts and pulmonary infarcts.

DR. JAMES H. MEANS: I saw this patient over a period of years in my office, and then I saw him in consultation with his local physician at the time of his last illness and cared for him in the hospital. There are a number of points I should like to mention. Dr. Sprague asked about the heart condition back in 1933. I do not know to what that 42 rate was due, or from where that note came. The chart showed a rate of about 60, and the electrocardiogram taken in 1933 reads: "Normal rhythm; heart rate of 65; P, Q, R, S and T waves normal in all leads; a tendency to very slight left-axis deviation, well within normal limits. Lead 3 was the unstable lead and varied some with respiration."

During the last illness there were several features which are worth going over. He had about as troublesome Cheyne-Stokes breathing as I have seen. That was the cause of his distress. He would sleep during the apnea and have bad dreams, and then would wake up in terror. Dr. Cobb saw him with me. He might comment on that part of it.

Dr. Sprague has considered the possibility of some unsuspected lesion. So did we. We thought of cancer on account of the weight loss but could not find any evidence and finally concluded he did not have it.

The findings in the left chest are worthy of comment. For the few days before he died he had pain on breathing and I examined the chest carefully. He had an x-ray examination shortly before death which was not very helpful, but I did wonder if he had some queer lesion in the left chest. I did not have the faintest idea what it was, because I could not find any physical signs, but it turned out that there was something peculiar there that we shall hear about later. He also had some swelling of the left arm. The pain in the left chest and arm made one wonder what was going on in the left chest or mediastinum. Of course Dr. Sprague has had the advantage of

postmortem x-ray films which I did not have when I made the following note the day he died. I predicted: "The pathologist will find a heart only slightly enlarged, if at all, with narrow coronaries and old infarcts. Some degree of fibromyocarditis and general arteriosclerosis will be present and in the main I expect there will be found extensive arteriosclerosis with thrombosis and softening in some silent area of the brain. Slight general anasarca will be present. There will probably be hypostatic pneumonia, not very marked, at each base. I am aware of no other lesion." The mental picture made me think there must be a lesion in the brain, which I presumed was sclerotic in origin.

DR. STANLEY COBB: I agree absolutely with Dr. Means's diagnosis. I might add about the brain that you may often have symptoms like these and at autopsy not have any recognizable lesion in gross; there are hardening of the arteries and areas of relative ischemia, but no areas of softening. On microscopic examination you ought to find a loss or abnormality of the nerve cells in some localized area. That should explain everything except his rather marked muscular twitchings. They were unusual in lasting for a long time. I do not know of anything that explains them satisfactorily, and I suppose we must fall back on the theory of relative ischemia of the brain for a long while, because of the hardening of the arteries.

CLINICAL DIAGNOSES

Cardiac infarction, old.
Arteriosclerosis.
Cerebral thrombosis, with softening.
Hypostatic pneumonia.

DR. SPRAGUE'S DIAGNOSES

Arteriosclerotic heart disease, with congestive failure.
Coronary occlusion (probably multiple).
Multiple pulmonary infarcts.
Minor occlusions of cerebral vessels.

ANATOMICAL DIAGNOSES

Arteriosclerosis, marked, coronary, cerebral and aortic.
Coronary thrombosis, old and recent.
Aneurysms, arteriosclerotic, right coronary and left internal iliac arteries.
Infarct of heart.
Hypertrophy of heart.
Pulmonary embolism, with pulmonary infarction.
Bullous emphysema, left lower lobe.
Diffuse cerebral atrophy.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This man showed a very extensive and diffuse arteriosclerosis. His heart was very much enlarged, weighing 650 gm. It showed severe coronary sclerosis affecting all branches, with two thrombi, a fairly fresh one in the left circumflex artery and an older one in the main right coronary artery. The latter artery was quite unusual in that it showed a fusiform aneurysm 1.2 cm. in diameter and 1.5 cm. in length which was completely filled with a partially organized thrombus. There was a large area of infarction at the apex and a still unorganized overlying thrombus, which was consistent with a duration of six weeks as suggested by the history. The left auricle contained a mural thrombus which might well have been the source of peripheral emboli but was not, so far as we could discover. The episode of circulatory difficulty in his toe, going back to the earlier admission, was probably explained by an aneurysm of the iliac artery which contained a thrombus, and I imagine that at some earlier period a small embolus broke off from this and was swept down to a small vessel of the foot. The lungs proved interesting. They showed complete infarction of both lower lobes, and on the left the picture was complicated by the fact that there was a huge emphysematous sac which overlay the infarct. It must have made considerable difference in the physical signs over that area and also served to confuse the x-ray picture. There were multiple pulmonary emboli to correspond with the areas of infarction. The brain showed a severe, rather diffuse arteriosclerosis, with evidence of diffuse atrophy. Perhaps Dr. Kubik will tell us more.

DR. CHARLES S. KUBIK: The ventricles were twice the normal size, and the convolutions showed atrophy. There was no infarction that one could see with the naked eye.

DR. MEANS: Just what was the brain lesion?

DR. MALLORY: A diffuse cerebral atrophy, which I should think was without much question based on severe arteriosclerosis.

DR. MEANS: Is that the sort of thing that precedes or takes the place of softening?

DR. MALLORY: The latter I think. Most of the cases in which we have seen such a picture have had pretty diffuse cerebral sclerosis, have they not, Dr. Kubik?

DR. KUBIK: Yes; one is likely to find numerous small infarcts with the microscope and sometimes can see them with the naked eye. I do not believe there was anything one could see with the naked eye in this case, however.

DR. MEANS: In regard to the size of the heart, I could not make out any great enlargement on

physical examination and was influenced by the statement of the radiologist that the heart shadow was indistinctly seen through the dull area and appeared to be only slightly enlarged. The patient was too sick for a seven-foot film.

CASE 25022

Presentation of Case

A seventy-seven-year-old, white, Canadian night watchman entered the hospital with the complaint of vomiting and hematemesis of four weeks' duration.

Seven years before entry he had had a "heart attack" characterized by breathlessness and generalized edema. He remained in bed for three weeks and two weeks later returned to work. He was given digitalis for the first month. He continued to be somewhat dyspneic but was able to work until two years before entry, when he fell, striking his right chest. He stayed in bed for two days but was unable to return to work because of dyspnea and ankle edema. His physician put him on a regime of restricted activity, with digitalis and Salyrgan medication, and he remained fairly well until six months before entry. At that time he suddenly developed pain in the left eye and soon was unable to see with it. For several years the vision in his right eye had been rather dim. Four weeks before entry he had had two episodes of vomiting. The vomitus contained gross blood. However, his appetite and digestion appeared to be unimpaired. Three weeks before entry he had again vomited clots of blood, and this was repeated one week later. During the two weeks before entry his appetite was poor, and his bowel movements were not so regular as they had been previously. During the recent period of his illness he had become pale and had shown some mental disorientation and loss of memory. On two occasions about seven months before entry he had had very severe nosebleeds.

His past history and family history were essentially negative. He had traveled all over the world as a seaman until he was thirty years old. He denied taking any alcohol.

Physical examination revealed a very pale, somewhat dyspneic, emaciated old man, lying flat in bed in no great discomfort. The veins of the neck were distended, and the left eyelid drooped. The lungs showed coarse moist rales at both bases. The heart was very much enlarged to the left, with a harsh systolic murmur heard loudest at the aortic area. The blood pressure was 140 systolic, 90 diastolic, and the pulse had an alternating quality. The liver was enlarged and somewhat tender. The abdomen was slightly tender throughout, but no masses were felt. The rectal examination was negative. There was pitting edema of the lower legs and feet, and the genitalia were somewhat edematous.

The temperature was 97°F., the pulse 75. The respirations were 20.

The urine had a specific gravity of 1.018 and contained a trace of albumin and occasional casts. The blood showed a red-cell count of 1,200,000 with 22 per cent hemoglobin, and a white-cell count of 11,000 with 78 per cent polymorphonuclears. The guaiac test on the stool was 2+. The nonprotein nitrogen of the blood was 117 mg. per cent.

On the second day a transfusion was given, but after 400 cc. of blood had been injected the patient began to cough and developed rales in the upper lung fields. He recovered from this and his condition remained about the same until the fourth day when, after exerting himself to sit up, he suddenly fell back, gasped a few times and died.

Differential Diagnosis

Dr. Richard J. Clark: We are confronted with an elderly man in the degenerative-disease age group. He had had a history of cardiovascular disease of seven years' duration, apparently with acute congestive heart failure seven years before death. This was followed by temporary improvement and then recurrence of failure, which was slowly progressive, with limitation of activity.

Six months before entry he developed sudden pain in the left eye followed by failure of vision. There is little to indicate just what occurred. It might have been acute glaucoma but more likely was an acute vascular accident, such as an embolus in the central artery or a venous thrombosis.

Four weeks prior to entry we have the onset of his terminal situation of vomiting and hematemesis. The vomitus contained large amounts of blood and clots. With the onset there was no story of nausea, abdominal pain or indigestion. The vomiting was spontaneous and seemed dependent on blood in the stomach. There is no other history of a bleeding diathesis, except for two severe nosebleeds seven months before which may well have resulted from hypertension.

On examination there was evidence of cardiac enlargement and failure. The blood pressure was relatively normal, but we may well assume that it was considerably elevated prior to his cardiac failure and repeated hemorrhages. His liver was enlarged and slightly tender. Apparently no spleen was felt.

The urine showed a good concentration, but

his nonprotein nitrogen was 117 mg. per cent. This may represent, in part at least, an extrarenal azotemia dependent on cardiac failure, blood and electrolyte loss and possibly liver disease. There was a profound anemia. We are told nothing about the blood smear, platelets or bleeding time, which helps us little toward a possible diagnosis of primary blood dyscrasia. Therefore we may reasonably assume that this was a severe secondary anemia.

Following transfusion the patient apparently developed acute pulmonary edema. His exodus was probably cardiac, although the possibility of a pulmonary embolus must be entertained.

The chief problem here is that of the cause of the hematemesis. This was gross acute bleeding. It might have come from a gastric or duodenal ulcer, but such repeated bleeding would seem unlikely in the complete absence of other symptoms of such a disorder. With cancer of the stomach the bleeding is more likely to be an oozing, with coffee-grounds vomitus. Acute gastritis should give other symptoms and bleeding in smaller amounts. There is no evidence for a primary blood dyscrasia. Such a massive degree of bleeding from a chronic Bright's disease would be unusual. In an old man with chronic vascular disease the possibility of an aneurysm's rupturing into the esophagus might be considered, but we should expect one profuse fatal hemorrhage with this condition. Why are we told of the blow to the right chest? Could he have developed a traumatic diaphragmatic hernia, with bleeding resulting from this? There are no other symptoms that point in this direction, and I believe such a diagnosis is unlikely.

The most probable cause of this bleeding is from esophageal varices dependent on a portal cirrhosis of the liver. The type of bleeding and the patient's general state fit with this. We should like to have had an alcoholic history, a description of dilated abdominal veins and possibly an enlarged spleen. There was no ascites or jaundice, but this need not deter us from the diagnosis. I may be wrong; the enlarged liver may be one of chronic passive congestion, and the bleeding may depend on passive congestion, with bleeding from an abnormal plexus of veins. However, lacking any x-ray or further data, I shall make a diagnosis of cirrhosis, with esophageal varices.

I believe a very much hypertrophied heart of the hypertensive type with coronary sclerosis will be found. Because of the harsh systolic murmur in the aortic area, calcification of the aortic valve is to be suspected, or possibly marked dilatation of the aorta. There will be acute and chronic passive congestion, together with generalized arteriosclerosis and also nephrosclerosis.

Clinical Diagnoses

Hypertensive and coronary heart disease with congestive failure.
Chronic vascular nephritis with uremia.
Hematemesis, etiology undetermined.
Secondary anemia.
Generalized arteriosclerosis.

Dr. Clark's Diagnoses

Hypertensive heart disease, with cardiac hypertrophy.
Coronary sclerosis.
Calcification of aortic valve?
Congestive failure, acute and chronic.
Generalized arteriosclerosis.
Nephrosclerosis.
Portal cirrhosis.
Esophageal varices.

Anatomical Diagnoses

Cardiac hypertrophy, hypertensive type.
Calcification of cusps of aortic valve, slight.
Arteriosclerosis, generalized.
Nephritis, chronic vascular, marked.
Hydrothorax, bilateral.
Chronic passive congestion.

Pathological Discussion

Dr. Tracy B. Mallory: This is the type of case that is apt to be a little disappointing, but I think is, nevertheless, worthwhile presenting every once in a while. All Dr. Clark's predictions are correct except as regards the cirrhosis of the liver and the cause of the hematemesis. Absolutely nothing was found to explain the latter. We see, on the average, one case a year of very severe hematemesis for which we are unable to find a cause. What the explanation of such cases is, I have no idea. It is not inconceivable, I suppose, for a man to have a nosebleed in his sleep and wake up and vomit blood.

He did have a very big heart, weighing 700 gm. He had some calcification of the aortic cusps. There was no real aortic stenosis, however. There was a point omitted in the physical examination that should have been recorded. The aortic second sound was louder than the pulmonic and not diminished as it probably would have been with true aortic stenosis. The lungs showed passive congestion. The kidneys showed rather marked nephrosclerosis and also a very severe cystic degeneration of the type that we see in elderly people —an entirely different type of cyst from that of the congenital polycystic kidney. In these older

people it is easy to prove that the cysts develop from glomerular capsules, presumably because of a blocked tubule. Bowman's capsule gradually dilates; the glomerulus shrinks to smaller and smaller proportions and finally disappears entirely. In the congenital polycystic kidney, the cysts have nothing to do with Bowman's capsule, and their origin is entirely unknown.

DR. ALLEN G. BRAILEY: Was it an anginal death?

DR. MALLORY: He had very good coronary arteries and we cannot assume that it was an anginal death.

DR. JOHN D. STEWART: How large was the liver?

DR. MALLORY: Moderately enlarged, due entirely to chronic passive congestion.

DR. JOHN W. ZELLER: What was the cause of death?

DR. MALLORY: I should say cardiac decompensation and uremia. Why it was sudden, I am not sure; but in a man with chronic nephritis of this type a nonprotein nitrogen of 80 mg. per cent is in the uremic level.

DR. RICHARD CHUTE: The anemia was secondary to the vomiting of so much blood rather than secondary to the renal condition?

DR. MALLORY: It could have been due to either. I have no way of distinguishing. Probably the two were cumulative in their effect.

A PHYSICIAN: Was there any antemortem diagnosis of the eye condition?

DR. MALLORY: There is no note. He was in the hospital a short period, and no eye consultant had seen him. We did not have permission to examine it postmortem.

DR. BERNARD JACOBSON: Was the bone marrow normal?

DR. MALLORY: No; it was hyperplastic so far as the vertebrae were concerned.

DR. JACOBSON: It was not suggestive of pernicious anemia?

DR. MALLORY: Not in the slightest respect.

DR. THORNTON SCOTT: What kind of heart disease did he have?

DR. MALLORY: Straight hypertensive heart disease, I should imagine. The kidneys certainly connote hypertension. Clinically we have nothing except a slightly elevated diastolic pressure on the final entry to give evidence, but it is very common in hypertensive disease to have the blood pressure fall terminally.

DR. WYMAN RICHARDSON: A blood pressure of 140 systolic, 90 diastolic, is quite high for a man with a red-count of 1,200,000. It is almost hypertension in itself.

DR. MALLORY: Yes.

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THE LICENSING OF HOSPITALS

There is a widespread conviction that the relation between physician and patient is of such an intimate and personal character that complete governmental control of the practice of medicine is chimerical. But there recurs constantly the question of whether less than complete control should be extended in some specific field of medicine. It is difficult to establish a general principle and to apply it wisely, so that before attempting to solve the problem for any limited field one should endeavor to discover the facts of practice in that field, the abuses, if they exist, the harm resulting and, finally, the remedy or remedies. Comparison with other fields and analogous problems should be made.

The abuses possible in uncontrolled hospitals for patients needing the care of a psychiatrist are too well known to demand a reopening of the question of whether such institutions should be licensed. In Massachusetts, they have all been placed under the Department of Mental Health, even though they are privately owned.

The need for the protection of women during childbirth has been recognized formally to the extent of requiring a license from the Massachusetts Department of Public Welfare for an institution which cares for such patients. Infants and children can no longer be "farmed out" as formerly, and the Commonwealth carefully supervises certain aspects of the care of these wards.

In the case of surgery, however, there is almost no supervision other than that the hospital building must meet the regulations of the local fire department. The most serious defect is that any physician licensed by the Board of Registration in Medicine may practice surgery. The candidate may be a psychiatrist of thirty years' practice, who has never seen an operation since he left the medical school. Or he may be a neophyte, just graduated from medical school, who has never actually participated in an operation and who failed miserably in the examination in surgery given by the Board, but whose general average was at the passing level. Both alike are free to operate if they see fit.

What may such a physician do? He may rent a small dwelling house for a hospital, employ a nurse, registered or unregistered, who will be superintendent, head nurse in the operating room and first assistant at all operations; another nurse, registered or unregistered, who will be night supervisor and extra nurse in the operating room; and a general-duty domestic servant, who will also cook. The surgeon may use some non-inhalation form of anesthesia and then perform abdominal operations, such as removal of the appendix, without the assistance of another physician. He may make, or fail to make, such records as he sees fit. He may falsify records and diagnoses and causes of death. He may have a showy array of therapeutic and laboratory apparatus and he may go through the gestures of making applications and examinations and writing down suitable results, which are impressively gone over with the patient's family, especially if death ensues, as indicating that everything humanly possible was done. If by chance

the physician is a clever operator, a clever salesman and a clever rascal who knows how to cover his tracks, what is the likelihood of his being discovered?

If by chance the physician is an abortionist who keeps careful and minutely detailed falsified records of examinations which indicate that the patient was not pregnant, even to a negative Aschheim-Zondek test and a notation that the doctor told the patient that she was not pregnant, and if the patient leaves the hospital in five or six days, satisfied, is there any likelihood of detection?

If the surgeon operates without consultation, never benefiting by the opinion of a pathologist, destroying without record or with falsified record, all tissue removed at operation, he may perform an enormous number of unnecessary operations and do untold harm. Thus, the unscrupulous and clever surgeon constitutes one of the most serious menaces in the care of the sick. Conscience and fiduciary responsibility are for him non-existent.

There arises also the question of whether all hospitals should be licensed, not merely those in which surgical operations are performed. Practically, the separation of hospitals into two such groups is impossible. Surgery should be regarded merely as one method of therapy. Pneumonia or typhoid fever or any one of a number of other medical diseases may develop complications demanding surgical treatment. To attempt to move the patient to another hospital might prove fatal and certainly would be dangerous.

For the improvement of medical care all hospitals should be licensed and all surgery should be checked in such a way that it is a matter of record that a definite diagnosis was made, that treatment was carried out by competent persons under reasonably satisfactory conditions for good surgery, that certain conditions were found at operation and that all tissue removed was examined in the laboratory by a competent pathologist.

In all first-class hospitals these have been among the minimum requirements for years, and the public has no conception of how much benefit it has received from the standardization of hospitals which, under the auspices of private agencies, has made such progress in the last quarter of a century. Now that private initiative has shown the way, public control by licensing of all hospitals may justly be required for the protection of the public. The members of the medical profession, who know not only the possibilities for abuse but also the actual abuses, should lead the way in advocating this necessary advance.

PHYSIOLOGICAL RESEARCH

THE lecture by Professor Meyerhof on the chemistry of the anaerobic recovery of muscle, which appears in this issue of the *Journal*, is an outstanding example of sustained and integrated physiological research. Its interest to the physician does not depend on a complete understanding of the complex chemical reactions that are discussed. What will appeal to the physician is the bird's-eye view of the nicety with which chemical and physical in vitro experiments have been correlated with the changes occurring in the physiologic processes of functioning tissue. The physician appreciates that the practical application of this knowledge to human subjects has already advanced our understanding of the physiology of exercise. He knows that the muscular dystrophies and diabetes mellitus involve deranged metabolism of creatine, phosphates, lactic acid and glucose. But the work reviewed by Professor Meyerhof shows that muscular metabolism not only involves these familiar compounds, but also depends on a whole new group of active intermediary products. These substances, which appear, split up and are resynthesized, are essential to muscular activity. Their discovery is as fundamental as that of the hormones or the vitamins. This new knowledge is particularly important to the physician, who continually attempts to comprehend and control various aspects of cellular activity in patients.

As the physician thinks of patients with perhaps a better understanding of these new factors he may see new ways of attacking clinical problems. Indeed, his clinical material may provide him with means of extending the knowledge of the physiologist that might never come to the latter's attention.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

PLACENTA ACCRETA

The patient was a thirty-eight-year-old primigravida, whose last menstrual period began April 14, 1937, and who was due to be confined January 21, 1938. When first seen, at seventeen weeks, her uterus was considerably larger than it should have been on the basis of her dates. Her pregnancy was uneventful until one week from term, when she had an elevation of blood pressure to 150 systolic, 100 diastolic, at which time her ankles were swollen and her urine showed a trace of albumin. Late in pregnancy a 5-cm. uterine mass, probably a fibroid, was palpated to the left and below the umbilicus.

Although labor pains began January 23, she did not begin to show dilatation of the cervix until four days later. The next day the membranes ruptured spontaneously and twenty-four hours later an infant, weighing 8 pounds, 10 ounces, was delivered following a lateral episiotomy. The placenta failed to separate, and so the patient was returned to her room. There was no external bleeding or evidence of accumulation of blood in the uterus. The latter reached nearly to the right costal margin and revealed another 5-cm. mass, this one attached to the fundus. After fourteen hours of failure of the placenta to separate, the patient was prepared for exploration of the uterus, a diagnosis of placenta accreta having been made. She was in good condition, with a blood pressure of 140 systolic, 84 diastolic, and a pulse of 96 to 124. Under nitrous oxide, oxygen and ether anesthesia the vulva and vagina were prepared with mercurochrome acetone and mercurochrome respectively. The hand was introduced into the fundus of the uterus, and numerous intramural fibroids were encountered. The placenta was definitely adherent and could not be removed without using more force than was justifiable. The patient was therefore prepared for laparotomy. A uterus which contained multiple fibroids was then removed supravaginally, leaving both tubes and ovaries.

Her postoperative course was complicated by a purulent vaginal discharge, beginning on the ninth day, although this had largely subsided by the time she left the hospital. Her temperature ranged from 99 to 101°F. up until the sixteenth day, and there was a moderate amount of postoperative abdominal distention. She was discharged well on the twenty-first postoperative day.

The pathological examination revealed a postpartum uterus with placenta attached, the whole specimen measuring 21 by 10 by 13 cm. There were many fibroid tumors distorting the specimen, the principal ones being as follows: a subserous one, 9 by 6 by 6 cm., at the right cornu; a subserous one, 3 by 3 by 1 cm., at the fundus; and an intramural one, 5 by 5 by 4 cm., within the left lateral wall. There were six other similar tumors, all smaller, scattered throughout the rest of the organ. The placenta measured 14 by 13 by 11 cm. and was firmly adherent to the uterine wall by its margins and in portions of its fundal attachment. The myometrium at the fundus measured 12 mm. in thickness, although there was a cornual sacculation (diverticulum) whose wall was only 3 mm. thick. Gentle to firm traction on the placenta did not dislodge it.

The microscopical examination of numerous sections revealed the picture of partial placenta accreta, complicated by acute inflammation. The spongy decidua basalis was absent, but occasional small areas of fibrosed, compact decidua remained at the placental site. In general, however, the placental villi were attached directly to the myometrium, which showed fibrosis and a variable degree of acute and chronic inflammation. The placental tissue, which was of normal, mature type, showed infiltration by acute inflammatory cells. The amniotic and chorionic membranes were especially involved in this process, probably associated with premature rupture of the membranes together with retention in the uterus fourteen hours post partum. The decidua vera likewise was deficient in its spongy, glandular layer, while the compact portion was deficient and fibrosed and showed variable degrees of acute and chronic inflammation.

Comment. This case is of extreme interest because of the fact that it occurred in a primipara, there being only one other such patient in the literature. Furthermore, the association of a placenta accreta with fibroid tumors and a diverticulum is very rare.

A series of selected case histories by members of the section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the section.

DEATHS

DAVIS — FREDERICK D. DAVIS, M.D., of 233 Forest Park Avenue, Springfield, died December 31. He was in his fifty-fifth year.

Born in Blandford he graduated from the Westfield

schools, attended Amherst College for one year and received his degree from the University of Vermont College of Medicine in 1910. After serving his internship at the Backus Hospital in Norwich, Connecticut, he returned to Westfield and practiced medicine for five or six years. Dr. Davis went to Springfield in 1917 and specialized in neurology although he did some general practice. In 1929 he was made a member of the Mercy Hospital staff in Springfield.

Dr. Davis held memberships in the American Medical Association and the Massachusetts Medical Society.

His widow, his mother and two daughters survive him.

GREGG — Donald Gregg, M.D., of Wellesley, died January 6. He was in his sixtieth year.

Born in Hartford, Connecticut, he moved as a child to Colorado Springs, Colorado, attending the public schools there. He prepared for college at Cutler Academy, graduated from Harvard College in 1902 and received his degree from Harvard Medical School in 1907. He served his internship during 1908-1909 at the Massachusetts General Hospital, after which he served four years as resident physician of the Philippine General Hospital at Manila, Philippine Islands. During one year there he was assistant professor of tropical medicine at the University of the Philippines.

Dr. Gregg returned to the United States in 1912 and began practicing in Wellesley. He became associated with Dr. Channing in the direction of the Channing Sanitarium at Wellesley, taking full charge at the time of Dr. Channing's death in 1922.

Among his affiliations were memberships in the American Medical Association, Massachusetts Medical Society, American College of Physicians, American Neurological Association, American Psychiatric Association, New England Society of Psychiatry, Association for Research in Nervous and Mental Disease and American Psychopathological Association.

His widow, three brothers and three sisters survive him.

MORGNER — Richard A. Morgner, M.D., of Main Street, Fitchburg, died December 27. He was in his sixty-sixth year.

After graduating from Clinton schools, he completed the course at Massachusetts College of Pharmacy, and then worked for two years as a druggist that he might attend medical school. He received his degree from Tufts College Medical School in 1902. After interning at the Chelsea Marine Hospital and the Lynn Hospital, in 1904 he went to Fitchburg, where his record of deliveries won for him an award from Tufts College Medical School.

He was a member of the American Medical Association and the Massachusetts Medical Society and was also on the senior surgical staff at the Burbank Hospital.

His widow and two children survive him.

MISCELLANY

"YOUR HEALTH" BROADCASTS

The next series of "Your Health" broadcasts, sponsored by the American Medical Association and the National Broadcasting Company and heard over the Blue Network each Wednesday at 2:00 p. m., is entitled "Dodging Contagious Diseases." It consists of four broadcasts, the last three of which are as follows:

January 18. Scarlet Fever, Measles and Whooping Cough.
Modern attitudes toward these diseases; prevention by community co-operation.

January 25. Smallpox and Diphtheria.
Unnecessary diseases; preventable by immunization of infants.

February 1. Preventing Epidemics.
Reporting of cases, quarantine and other control measures.

NOTES

The following appointments to the staffs of the Harvard Medical School and the Harvard School of Public Health have been recently announced: Thomas R. C. Fraser, as research fellow in medicine, D.P.M. London '37; Alfredo Lanari, of Buenos Aires, as research fellow in physiology, M.D. Buenos Aires '34; Eric K. Cruickshank, of Aberdeen, Scotland, as research fellow in surgery, M.B., Ch.B. Aberdeen University '37; Maximilian G. Verlot, of Ghent, Belgium, as research fellow in surgery, M.D. Ghent '35; Adolph Meltzer, of New York City, as assistant in surgery, M.D. Cornell '34; Maurice H. Greenhill, as research fellow in psychiatry, M.D. University of Chicago '36; Nathan Gorin, of Boston, as assistant in child hygiene, M.D. Boston University School of Medicine '17.

The following fourth-year students in the Harvard Medical School have been elected to membership in the Harvard chapter of Alpha Omega Alpha: John Adams, Eben Alexander, Lemuel Bowden, Jerome Frank, Charles Jennings, Ferdinand McAllister, Max Michael, Arthur Pier, Frederick Ross, John Wilson and Lucius Wing.

On January 1, Dr. Joseph B. Howland retired as superintendent of the Peter Bent Brigham Hospital, having served in that capacity since May 1, 1919 — or nearly twenty years. He was succeeded by Dr. Norbert A. Wilhelm, a former assistant superintendent and, for the past two years, superintendent of the Butterworth Hospital, Grand Rapids, Michigan. Dr. Wilhelm graduated from St. Louis University School of Medicine in 1925.

CORRESPONDENCE

THE GREATER LAWRENCE MEDICAL ASSOCIATION

To the Editor: On December 14, the Greater Lawrence Medical Association held its second annual dinner. The guest speaker was Dr. Morris Fishbein, of Chicago, editor of the *Journal of the American Medical Association*, who spoke on "The National Health Program and American Medicine."

His talk was broadcast over two radio networks and I thought it would be of interest to the fellows of the Society to know the favorable reaction of the public to his remarks. Many messages of praise have come back to us, most of which say that the doctors have a case after all. In view of the constant and almost continuous deluge of propaganda against the physicians of this country in the daily press and the weekly and monthly periodicals, it must be indeed refreshing at times to hear the doctors' side of the story. I am fairly convinced that the medical profession has lagged in this respect and it is, therefore, pleasing to see that through the efforts of the Massachusetts Medical Society a series of articles is now ap-

pearing in the *Boston Evening Transcript*. This is good work, and too much of it cannot be done.

Yesterday the Greater Lawrence Medical Association invited Congressman Laurence J. Connery at a special meeting, which was attended by a large number of physicians. We presented our case to him in detail, and he apparently was very much impressed by our story. He said that, although many physicians had asked him to vote against socialized medicine, no group in his congressional district had up to this time taken the trouble to discuss the subject with him. He told us that he hoped that other organizations would get together with their congressmen, because he was sure that on their return to Washington the opposition would canvass every member of Congress.

N. F. De Cesare, M.D., *President*,
Greater Lawrence Medical Association.

Lawrence, Massachusetts.

NOTICES

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held on Tuesday, January 24, in the Peter Bent Brigham Hospital amphitheater (Shattuck Street entrance), at 8:15 p. m.

PROGRAM

Presentation of cases.
Some Clinicoroentgenological Correlations. Dr. Merrill C. Sosman and Dr. Samuel A. Levine.

Medical students and physicians are cordially invited to attend.

MEDICAL CLINIC AT THE PETER BENT BRIGHAM HOSPITAL

At 3:30 p. m. on Thursday, January 19, in the amphitheater of the Peter Bent Brigham Hospital, Dr. Samuel A. Levine, assistant professor of medicine, Harvard Medical School and senior associate in medicine, Peter Bent Brigham Hospital, will give a medical clinic. Practitioners and medical students are cordially invited to attend.

CENTRAL MASSACHUSETTS ALUMNI CLUB OF BOSTON UNIVERSITY SCHOOL OF MEDICINE

A symposium sponsored by the Central Massachusetts Alumni Club of Boston University School of Medicine will be held in the Worcester State Hospital Chapel (Administrative Building), Belmont Street, Worcester, on Wednesday, January 18, at 8:00 p. m.

The symposium "The Recent Epidemic, in Human Beings, of Encephalomyelitis in Massachusetts: A clinical, pathological and immunological study" will be given by Dr. Edward C. Smith, Dr. Charles F. Branch and Dr. LeRoy D. Fothergill.

Physicians, medical students and nurses are cordially invited to attend.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The next meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday evening, January 18. The Council will meet at 6:00; there will be an informal dinner at 6:30 in the Empire Room.

PROGRAM

Organic Arterial Disease (with colored slides). Dr. Edward A. Edwards. Discussion: Dr. Laurence B. Ellis.

All members of the medical profession are cordially invited to attend.

William D. McFee, M.D., *Secretary*.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held in the Mallory Amphitheater, Boston City Hospital, Monday, January 23, at 8:15 p. m.

PROGRAM

Clinicopathological Correlations. Dr. Soma Weiss.
Study of the Presystolic Murmur of Mitral Stenosis and the Factors Influencing the Intensity of the First Heart Sound. Dr. Eugene A. Stead, Jr.
The Effect of Anemia on the Heart, with Particular Reference to Electrocardiographic Changes. Dr. Laurence B. Ellis.
Influence of the Peripheral Circulation in the Upper Extremities on the Circulation Time as Measured by the Sodium Cyanide Method. Dr. Paul Kunkel.
Blood Flow and Vasomotor Reactions of the Hand, Forearm, Foot and Calf in Response to Physical and Chemical Stimuli. Dr. Eugene A. Stead, Jr.
Thrombosis of the Ductus Arteriosus with Embolic Manifestations. Dr. Blair V. Jager.
Gummatous Aortitis. Dr. William H. Gordon.

Edward F. Bland, M.D., *Secretary*.

NEW ENGLAND WOMEN'S MEDICAL SOCIETY

The annual meeting of the New England Women's Medical Society will be held at the Myles Standish Hotel, Thursday, January 19.

Hon. Paul Dever, attorney general of Massachusetts, will be the speaker.

A business meeting will be held promptly at 6:30 p. m. Dinner will be served at 7:15.

Mary I. Tompkins, M.D., *Secretary*.

MASSACHUSETTS MEMORIAL HOSPITALS

There will be a luncheon meeting of the surgical section in the Aid Association Room, Talbot Memorial, 82 East Concord Street, on Tuesday, January 17, at 12 o'clock noon.

Surgical deaths during the month of November will be discussed.

Milo C. Green, M.D., *Secretary*.

CARNEY HOSPITAL

The monthly clinical meeting and luncheon of the Carney Hospital will be held in Andrew Carney Assembly Room on Monday, January 16, at 11:30 a. m.

PROGRAM

Case reports.
Anesthesia in Abdominal Surgery. Dr. H. Bruce MacEwen. Discussion: Drs. Joseph Kennedy, H. L. Brayton and John S. Kelley.

Physicians and medical students are cordially invited to attend.

Roy J. Heffernan, M.D., *Secretary*.

BOSTON LYING-IN HOSPITAL

The next meeting of the Journal Club will be held on Wednesday evening, January 18, at 8:30.

Dr. Herbert Thoms, of the Yale University School of Medicine, will present a paper "The Obstetric Pelvis." Classification of the abnormal types, roentgenometry and its relation to labor will be illustrated by lantern slides and moving pictures.

Physicians and students are invited to attend.

DUNCAN E. REID, M.D., *Secretary*.

MASSACHUSETTS ITALIAN MEDICAL SOCIETY

The next meeting of the Massachusetts Italian Medical Society will be held on Friday evening, January 20, at the Hotel Kenmore, Boston, at 9:00.

PROGRAM

Business meeting.

Relations of the Dental Profession to the Medical Field. V. J. Pollina, D.M.D., president of the Italian-American Dental Society of New England.

Functions of the Board of Registration in Medicine. D. A. Costa, M.D.

Members of the medical and dental professions are cordially invited to attend.

CARL F. MARALDI, M.D., *Secretary*.

NEW ENGLAND PATHOLOGICAL SOCIETY

The next meeting of the New England Pathological Society will be held at the Mallory Institute of Pathology, Boston City Hospital, on Thursday evening, January 19, at 8:00.

Dr. Paul A. Younge will speak on "Pre-invasive Carcinoma of Cervix Uteri."

Physicians and medical students are cordially invited to attend.

GRANVILLE A. BENNETT, M.D., *Secretary*.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, JANUARY 16

MONDAY, JANUARY 16

*11:30 a. m. Carney Hospital. Monthly clinical meeting and luncheon. Andrew Carney Assembly Room.

TUESDAY, JANUARY 17

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Clinicopathological conference. Dr. Harold Wood. Discussion by Dr. Chester Keefer.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

12 m. Massachusetts Memorial Hospitals. Luncheon meeting of the surgical section. Aid Association Room, Talbot Memorial, 82 East Concord Street, Boston.

*12 m. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

WEDNESDAY, JANUARY 18

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Hospital case presentation. Dr. S. J. Thannhauser.

*12 m. Clinicopathological conference. Children's Hospital amphitheater.

*6 p. m. New England Society of Physical Medicine. Hotel Kenmore.

*8:30 p. m. Boston Lying-in Hospital. Journal Club meeting.

THURSDAY, JANUARY 19

8:30-9:30 a. m. Exchange visit, Surgical and Orthopedic Staffs of the Peter Bent Brigham and Children's hospitals, held this week at the Peter Bent Brigham Hospital.

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. The Management of Lacerations of the Perineum with Special Reference to Complete Lacerations. Dr. L. E. Phaneuf.

*3:30 p. m. Medical clinic at the Peter Bent Brigham Hospital.

6:30 p. m. New England Women's Medical Society. Myles Standish Hotel, Boston.

*8 p. m. New England Pathological Society. Boston City Hospital, Mallory Institute of Pathology.

FRIDAY, JANUARY 20

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Varieties of Thrombophlebitis and Their Relation to Embolism: Methods of prevention and treatment. Dr. John Homans.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

12 m. Clinical meeting of the Children's Medical Service, Massachusetts General Hospital, Ether Dome.

*9 p. m. Massachusetts Italian Medical Society. Hotel Kenmore, Boston.

SATURDAY, JANUARY 21

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Hospital case presentation. Dr. S. J. Thannhauser.

*10 a. m. - 12 m. Staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

SUNDAY, JANUARY 22

4 p. m. Illustrated, public health lecture, Faulkner Hospital, auditorium. Reasons for High Standards in Medical Education and Practice. Dr. Alexander S. Begg.

4 p. m. Free public lecture, Harvard Medical School, amphitheater of Building D. Cancer. Dr. Tracy B. Mallory.

*Open to the medical profession.

JANUARY 15 — Lecture at the Faulkner Hospital. Page 971, issue of December 15.

JANUARY 15 — Free Public Lecture, Harvard Medical School. Page 1056, issue of December 29.

JANUARY 15 — Beverly Hospital Public Health Lecture. Page 1056, issue of December 29.

JANUARY 16 — Carney Hospital. Page 83.

JANUARY 17 — Massachusetts Memorial Hospitals. Page 83.

JANUARY 17 — South End Medical Club. Page 42, issue of January 5.

JANUARY 18 — New England Society of Physical Medicine. Page 83.

JANUARY 18 — Boston Lying-in Hospital. Journal Club meeting. Notice above.

JANUARY 18 — Central Massachusetts Alumni Club of Boston University School of Medicine. Page 83.

JANUARY 19 — Medical clinic, Peter Bent Brigham Hospital. Page 83.

JANUARY 19 — New England Women's Medical Society. Page 83.

JANUARY 19 — New England Pathological Society. Notice above.

JANUARY 20 — Massachusetts Italian Medical Society. Notice above.

JANUARY 23 — New England Heart Association. Page 83.

JANUARY 24 — Harvard Medical Society. Page 83.

FEBRUARY 4, MAY 15 and 16 — American Board of Obstetrics and Gynecology. Page 451, issue of September 22. (*Application for admission to Group A examinations must be on file in the Secretary's office by March 15, instead of April 1 as previously stated.*)

FEBRUARY 9 — Pentucket Association of Physicians, 8:30 p. m., Hotel Bartlett, 95 Main Street, Haverhill.

MARCH 13 — Fourth Annual Postgraduate Institute. Page 938, issue of December 8.

MARCH 15, MAY 15, AUGUST 5 and OCTOBER 6 — American Board of Ophthalmology. Page 1013, issue of December 22.

MARCH 27-31 — American College of Physicians. Page 36, issue of July 7.

MAY 7-15 — International Congress of Military Medicine and Pharmacy. Page 501, issue of September 29.

MAY 15-16 — American Board of Obstetrics and Gynecology, Inc. Page 937, issue of December 8.

MAY 15-19 — American Medical Association, St. Louis, Missouri.

JUNE 6, 7, 8 — Massachusetts Medical Society. Worcester.

JUNE 26-29 — National Tuberculosis Association. Page 936, issue of December 8.

SEPTEMBER — Boston Psychoanalytic Institute. Page 450, issue of September 22.

SEPTEMBER 11-15 — American Congress on Obstetrics and Gynecology. Page 938, issue of December 8.

SEPTEMBER 15-28 — Pan-Pacific Surgical Association. Page 863, issue of November 24.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH

FEBRUARY 8 — Essex Sanatorium, Middleton. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. Edward Churchill. Subject: Surgical Treatment of Pulmonary Suppuration.

MARCH 1 — Lynn Hospital. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. John Rock. Subject: Endocrinology.

APRIL 5 — Addison Gilbert Hospital, Gloucester. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. Ethan Allan Brown. Subject: Allergy.

MAY 10 — Annual meeting. Salem Country Club, Peabody.

SUFFOLK

JANUARY 25 — Symposium on Diabetes. Dr. Elliott P. Joslin and associates, Boston Medical Library, 8:15 p. m.

MARCH 29 — Joint meeting with New England Pediatric Society, Boston Medical Library, 8:15 p. m. Program and speakers to be announced.

APRIL 26 — Annual meeting in conjunction with Boston Medical Library, at 8:15 p. m. Election of officers. Program and speakers to be announced.

WORCESTER

FEBRUARY 8 — Worcester State Hospital.

MARCH 8 — Worcester Memorial Hospital.

APRIL 12 — Worcester Hahnemann Hospital.

MAY 10 — Worcester Country Club — Annual meeting.

With the exception of the annual meeting in May, all the meetings begin with a supper at 6:30 p. m., which is followed at 7:30 p. m. by the business and scientific sessions.